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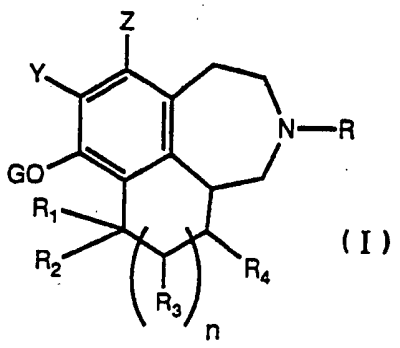
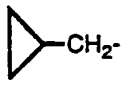
(54) Title: PERI-CONDENSED BENZAZEPINES



(I)



(a)

(57) Abstract

Compounds of formula (I) or a pharmaceutically acceptable salt thereof, wherein R represents H, alkyl, allyl, or (a); n represents 0 or 1; R_1 and R_2 may be the same or different and each independently represents H, OH, C_1-C_4 alkyl or Ar; with the proviso that R_1 and R_2 may not both be OH, and with the further proviso that when n is 0, R_1 is C_1-C_4 alkyl or Ar, R_2 is CH_3 and R_4 is H; R_3 and R_4 may be the same or different and each independently represents H or C_1-C_4 alkyl; G represents H, (R_5, R_6)NCO- or ArNHCO-; R_5 and R_6 may be the same or different and each independently represents H, C_1-C_4, alkyl, or Ar; Ar represents phenyl or substituted phenyl; Y and Z may be the same or different and each independently represents H, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, or C_1-C_4 haloalkyl are described. The compounds of formula (I) are useful as agents in the treatment of psychoses and drug dependence. The compounds of formula (I) also provide an analgesic effect in a mammal.

+ See back of page

+ DESIGNATIONS OF "SU"

Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

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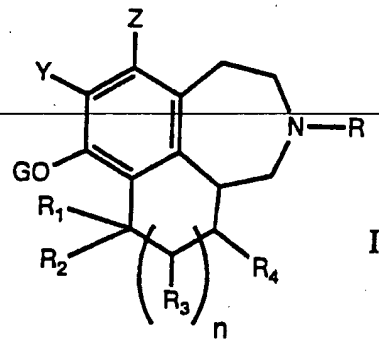
Peri-condensed benzazepines

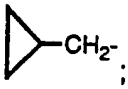
SUMMARY OF THE INVENTION

The invention relates to compounds of the formula:



I

or a pharmaceutically acceptable salt thereof, wherein

R represents H, alkyl, allyl or  ;

n represents 0 or 1;

R_1 and R_2 may be the same or different and each independently represents H, OH, C_1-C_4 alkyl, or Ar with the proviso that R_1 and R_2 may not both be OH, and with the further proviso that when n is 0, R_1 is C_1-C_4 alkyl or Ar, R_2 is CH_3 and R_4 is H;

R_3 and R_4 may be the same or different and each independently represents H or C_1-C_4 alkyl;

G represents H, $(R_5,R_6)NCO$- or ArNHCO-;

R_5 and R_6 may be the same or different and each independently represents H, C_1-C_4 alkyl, or Ar;

Ar represents phenyl or substituted phenyl;

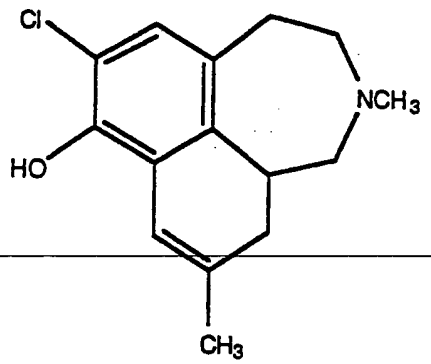
Y and Z may be the same or different and each independently represents H, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, or C_1-C_4 haloalkyl.

with the proviso that:

A. at least one of R_1, R_2, R_3 and R_4 must not be hydrogen; and/or

B. G must represent ArNHCO-, or (R_5, R_6)NCO- where at least one of R_5, R_6 represents Ar.

This invention also includes the compound of the formula



II

Preferred are compounds of formula I wherein n is 1.

Compounds of formula I wherein n is 1 and R is alkyl such as methyl are especially preferred.

Compounds of formula I wherein n is 1, R is methyl and Z is H or chloro are also especially preferred.

Compounds of formula I wherein n is 1, R is methyl and Y is H or chloro are also especially preferred.

Compounds of formula I wherein n is 1, R is methyl, Z is chloro and Y is chloro are also especially preferred.

Compounds of formula I wherein n is 1, R is methyl, Y is CH_3O-, HO-, CH_3-, or H- are also preferred.

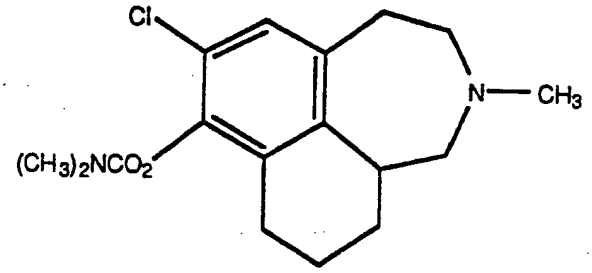
Compounds of formula I wherein n is 1, R is methyl and G is H are still also especially preferred.

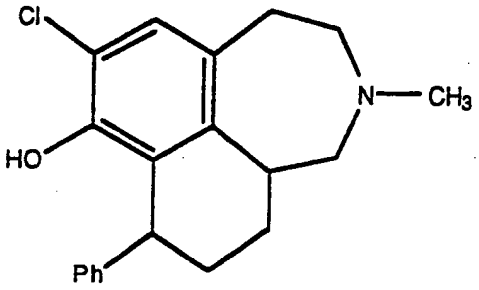
Compounds of formula I wherein n is 1, R is methyl and G is ArNHCO- wherein Ar is substituted phenyl are also especially preferred.

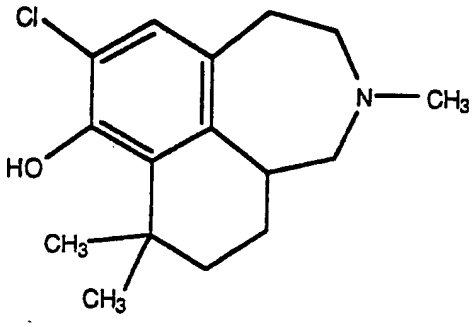
As used herein Ph denotes phenyl and i-Pr denotes isopropyl. Also as used herein, a broken line (‥‥) denotes a chemical bond below the plane of the page, while a solid line (——)

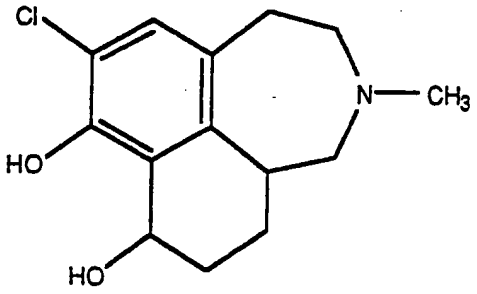
denotes a chemical bond above the plane of the page. Also as used herein, a squiggly line (~~~~) denotes a chemical bond whose stereochemistry is not known, or denotes a mixture of compounds wherein one compound has chemical bond of one stereochemistry, and the other compound has the chemical bond of the other stereochemistry

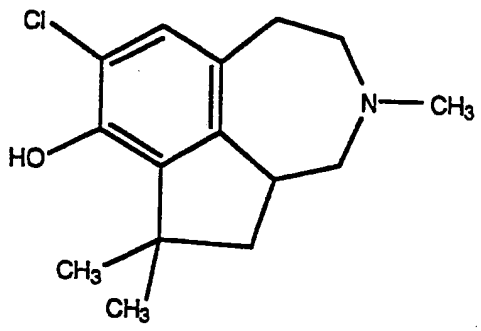
Exemplary compounds of the invention include:

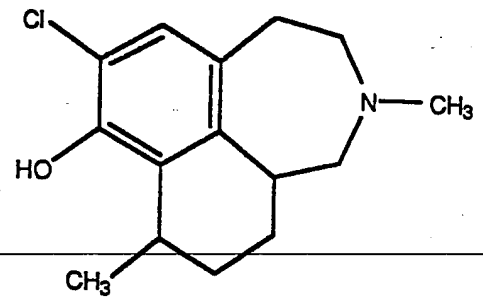












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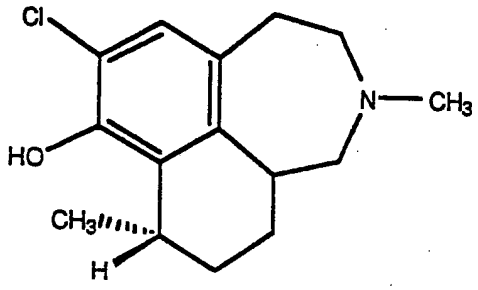

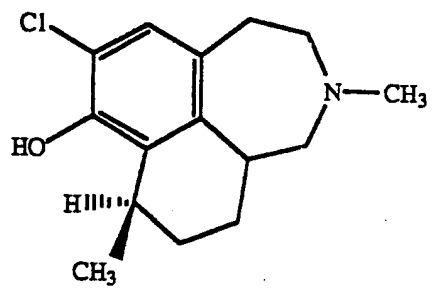

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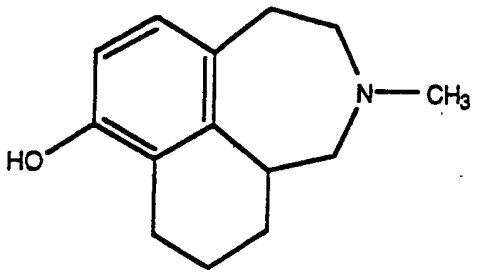
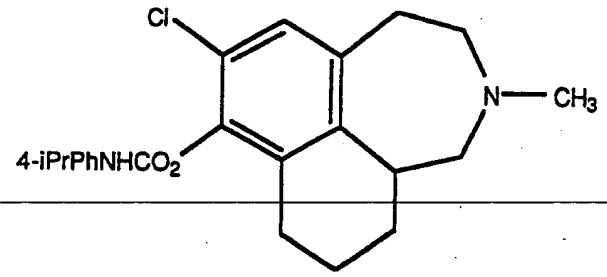
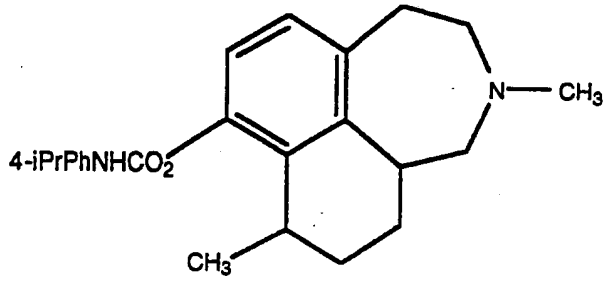
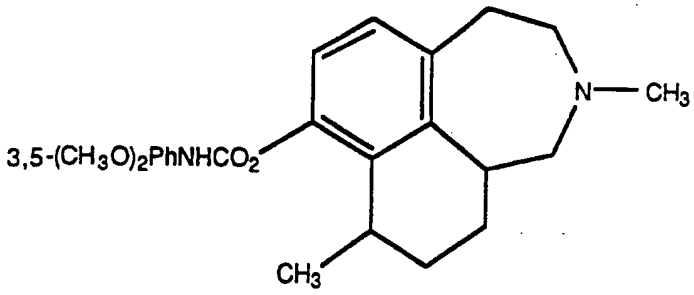
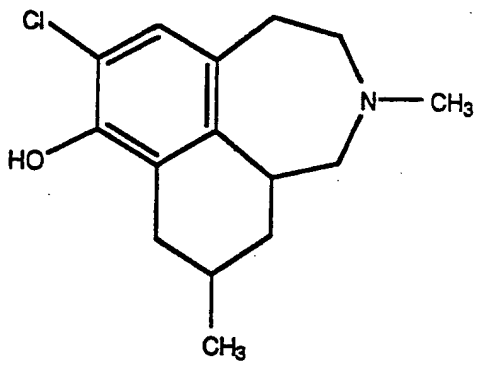
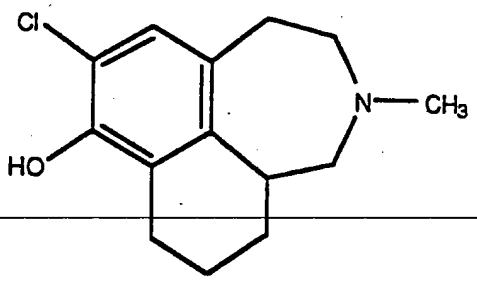

HO
N
CH3

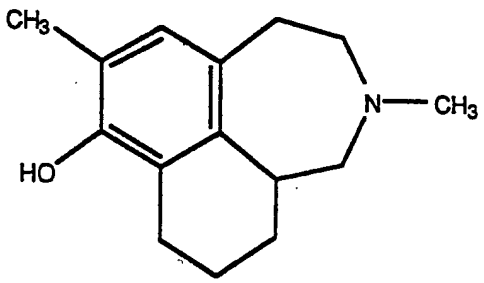

Cl
4-iPrPhNHCO2
N
CH3

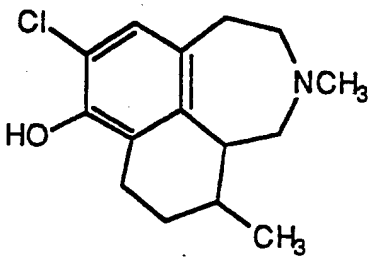

4-iPrPhNHCO2
N
CH3
CH3

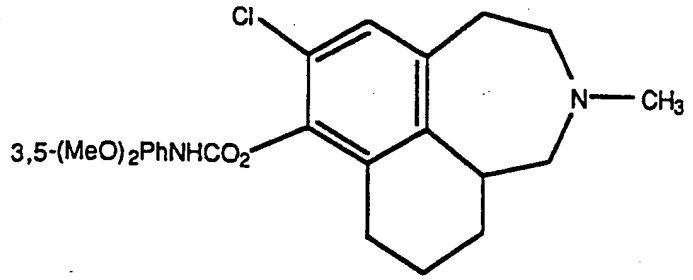

3,5-(CH3O)2PhNHCO2
N
CH3
CH3


Cl
N
CH3
HO
CH3

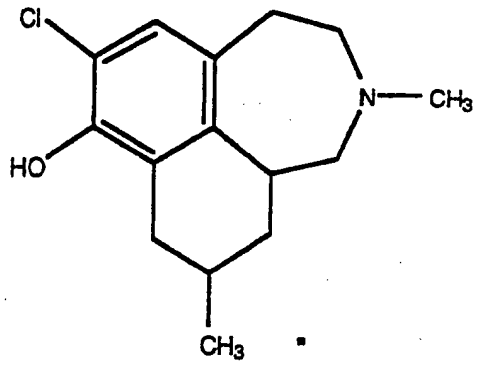

Cl
N
CH3
HO


CH3
N
CH3
HO

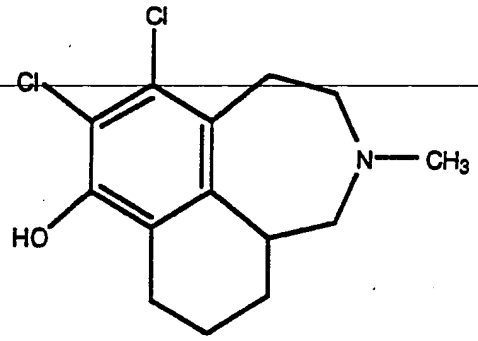

Cl
NCH3
HO
CH3


Cl
N
CH3
3,5-(MeO)2PhNHCO2

and



The most preferred compound of the invention is



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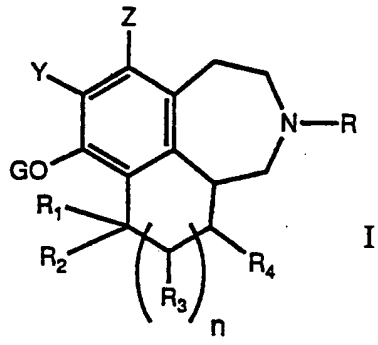
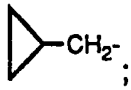
The invention also involves pharmaceutical compositions for treating psychoses comprising a compound of formula



I

or a pharmaceutically acceptable salt thereof, wherein

R represents H, alkyl, allyl or  ;

n represents 0 or 1;

R_1 and R_2 may be the same or different and each independently represents H, OH, C_1-C_4 alkyl or Ar, with the proviso that R_1 and R_2 may not both be OH, and with the further proviso that when n is 0, R_1 is C_1-C_4 alkyl or Ar, R_2 is CH_3 and R_4 is H;

R_3 and R_4 may be the same or different and each independently represents H or C_1-C_4 alkyl;

G represents H, $(R_5,R_6)NCO$- or ArNHCO-;

R_5 and R_6 may be the same or different and each independently represents H, C_1-C_4 alkyl, or Ar;

Ar represents phenyl or substituted phenyl;

Y and Z may be the same or different and each independently represents H, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, or C_1-C_4 haloalkyl in combination with a pharmaceutically acceptable carrier;

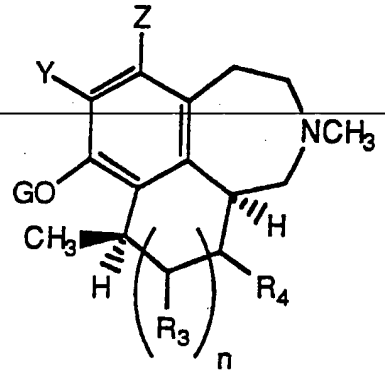
and a pharmaceutical composition for treating psychoses comprising a compound of formula II in combination with a pharmaceutically acceptable carrier;

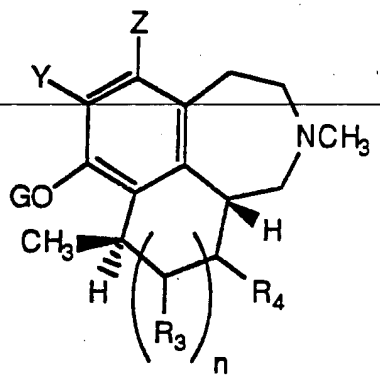
The invention also involves a pharmaceutical composition comprising a compound of formula I or II in combination with a

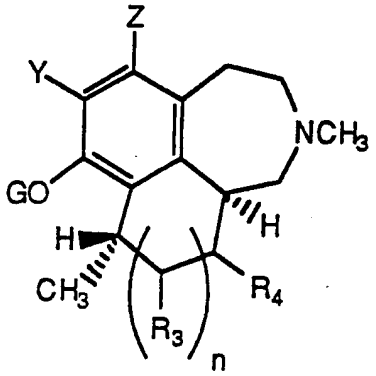
pharmaceutically acceptable carrier and methods for treating drug dependence, for treating a mammal suffering from a D1 dependent neurological disorder, and for providing analgesia in a mammal, which comprise administering to the mammal an effective amount of a compound of formula I or II for such purposes.

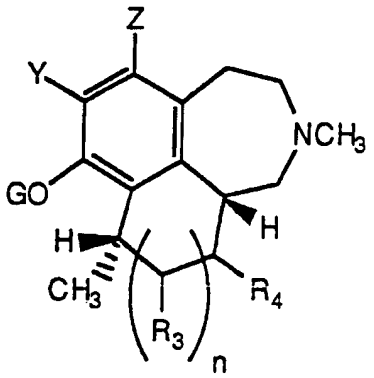
DETAILED DESCRIPTION OF THE INVENTION

It is noted that, when R_1 and R_2 on the same carbon atom are different, e.g., H and CH_3, respectively, stereoisomers of the following formulas exist:









All such isomeric forms and mixtures thereof are within the scope of the present invention. Unless otherwise indicated, the methods of preparation disclosed herein may result in product distributions which

include all possible structural isomers, although it is understood that physiological response may vary according to stereochemical structure. The isomers may be separated by conventional means such as fractional crystallization or HPLC (high performance liquid chromatography).

Compounds of formulas I or II can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of this invention. All such forms are within the scope of this invention.

The compounds of formulas I or II may form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms and are within the scope of this invention.

When utilized herein and in the appended claims, the following terms, unless otherwise specified, have the following meanings:

alkyl (including the alkyl portions of alkoxy, hydroxyalkyl haloalkyl, etc.) - represents a straight or branched, saturated hydrocarbon chain having from 1 to 8, preferably from 1 to 6, carbon atoms (The number of carbon atoms may be designated. For example, "C_1-C_4 alkyl" represents a straight or branched, saturated hydrocarbon having from 1 to 4 carbon atoms.);

alkoxy - repr sents an alkyl group attached to a molecule through an oxygen atom (alkyl-O-);

allyl - represents the groups $-CH_2-CH=CH_2$, $-CH=CH-CH_3$, or $-C(CH_3)=CH_2$;

halo - represents fluoro, chloro, bromo or iodo;

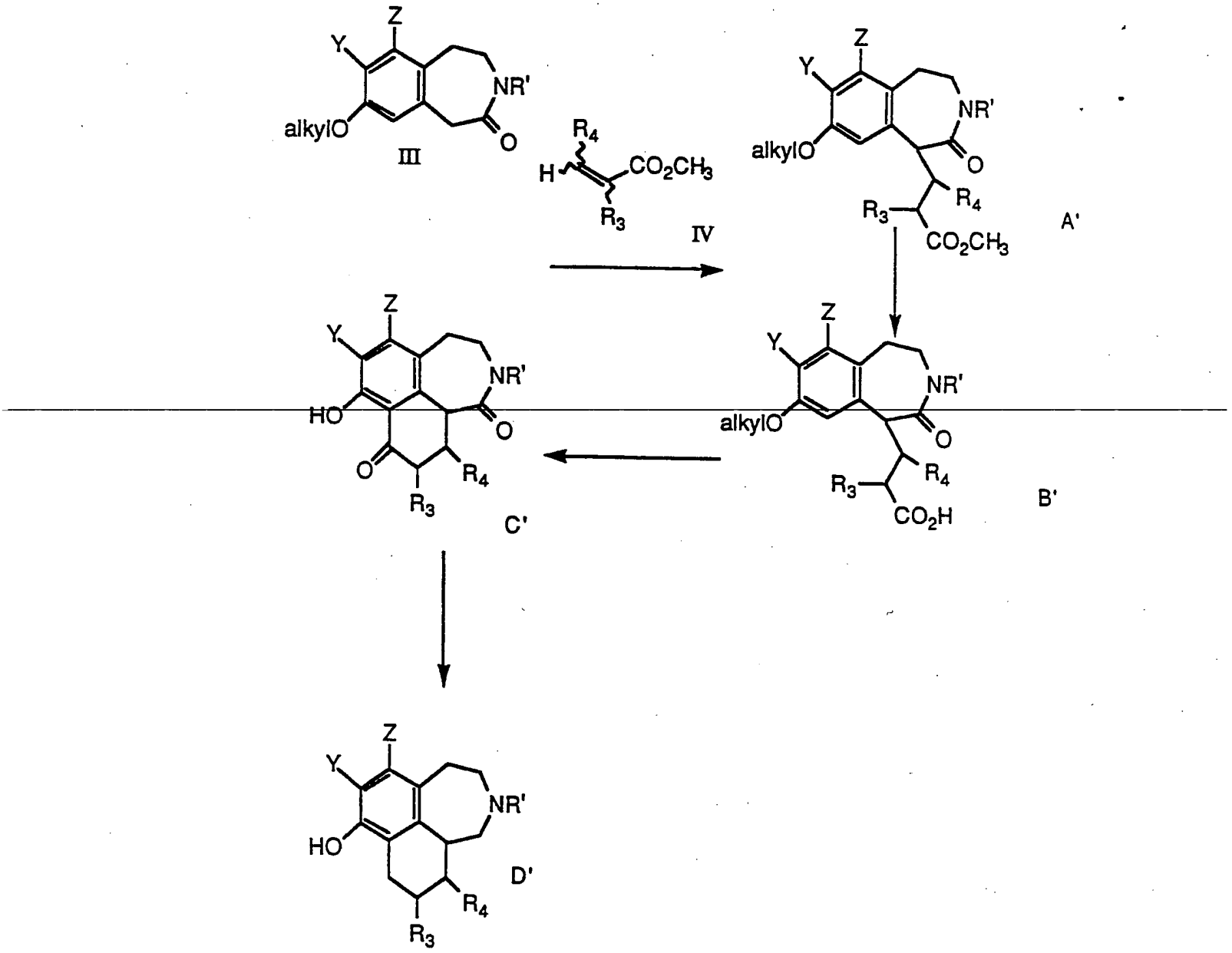
haloalkyl - represents an alkyl group as defined above wherein 1 to 3 hydrogens thereof have been replaced with a halo moiety, e.g., trifluoromethyl, 2-chloroethyl, etc.; and

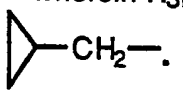
substituted phenyl - represents a phenyl group in which 1 to 3 hydrogen atoms thereof are replaced by the same or different substituents independently chosen from hydroxy, alkyl, halo, nitro, alkoxy, haloalkyl including trifluoromethyl, cyano, cycloalkyl, SH, or $S(O)_pR^a$ [wherein p is 0, 1 or 2 and R^a is alkyl].

As used herein degrees or "°" refers to degrees Celsius unless otherwise indicated.

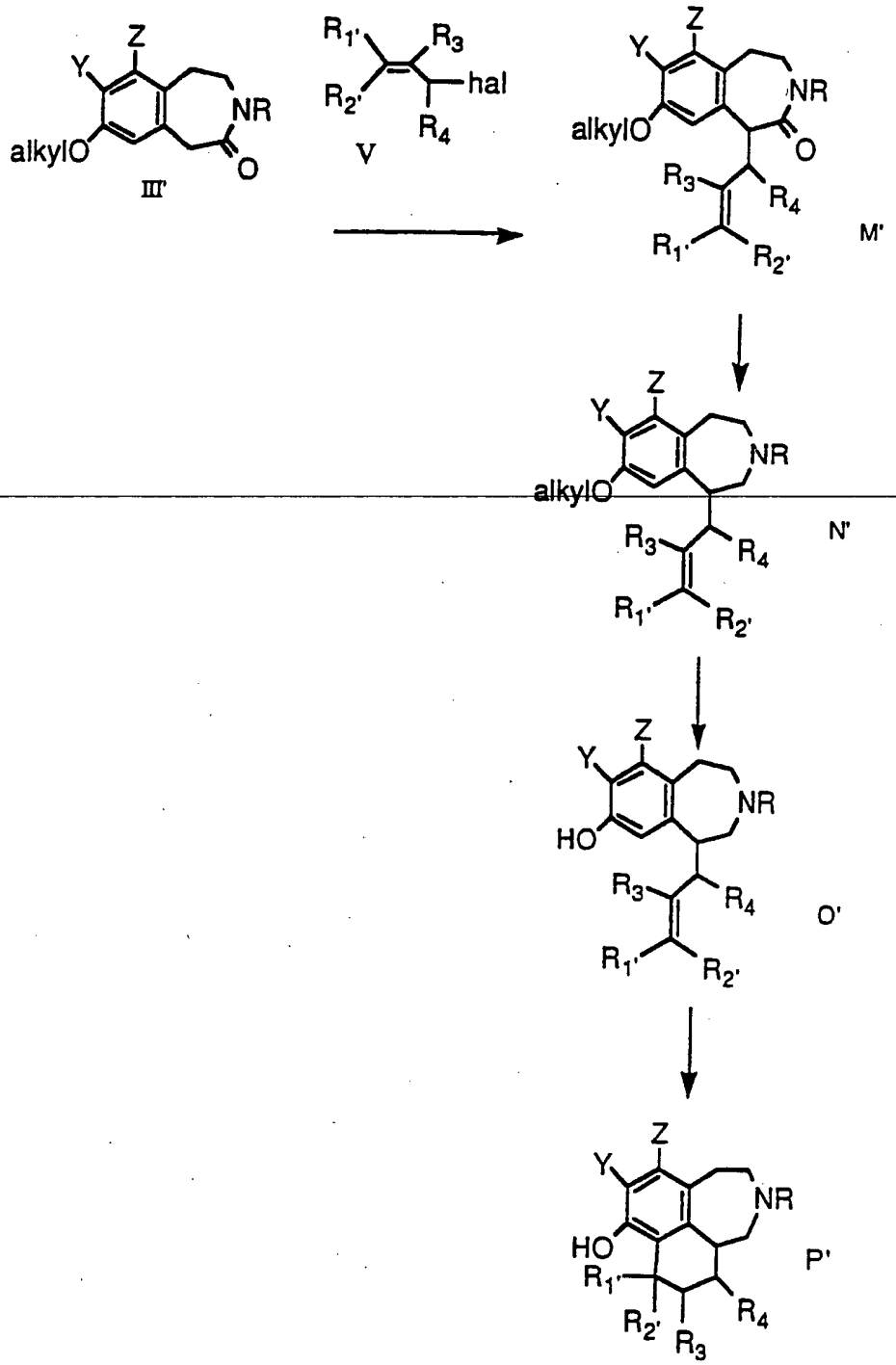
The compounds of formula I above may be prepared by the methods described below with reference to Schemes 1, 2, 3, and 4 wherein G, Y, Z and R, R_1, and R_2 are as defined above, unless otherwise indicated:

SCHEME 1



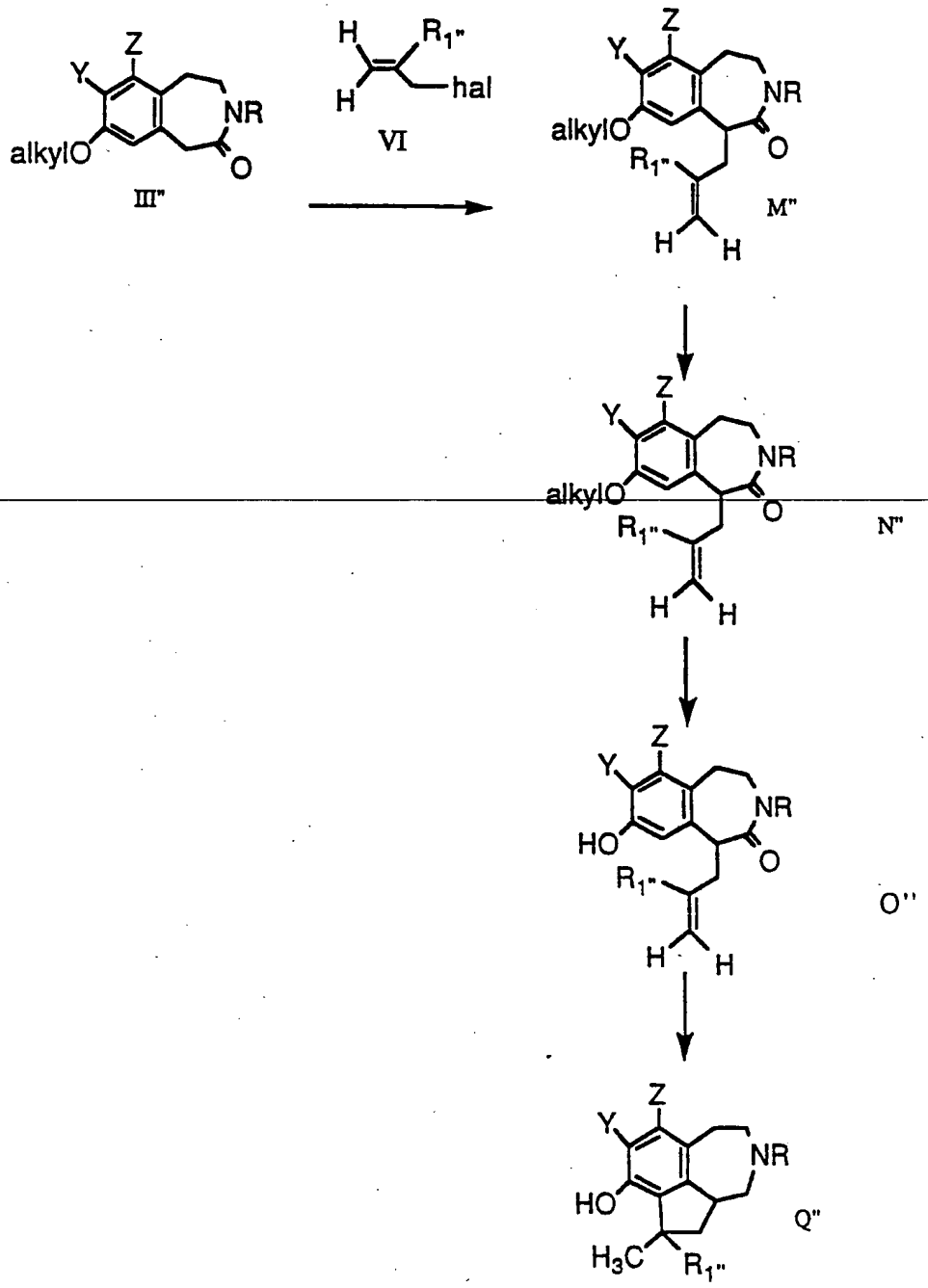
wherein R_3, R_4, Y and Z are as described above and R' is H, alkyl or  .

SCHEME 2



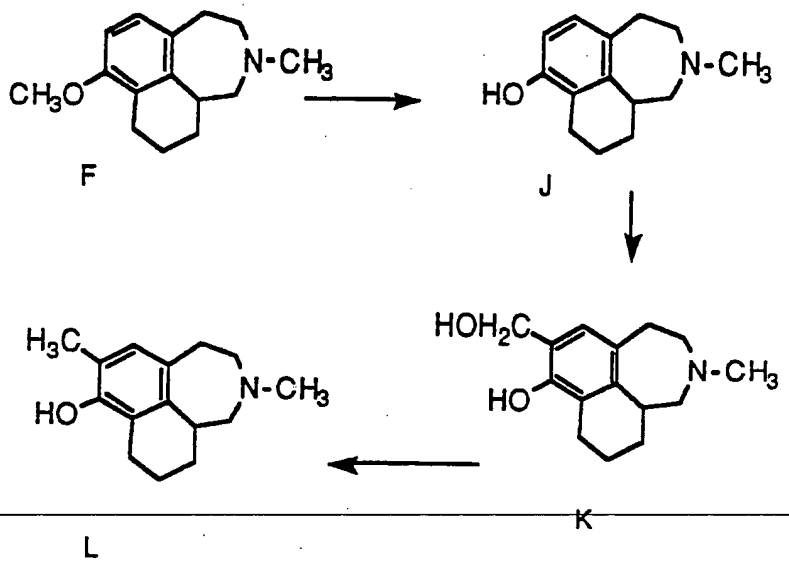
wherein R, R_3, R_4, Y and Z are as described above, and $R_{1'}$ and $R_{2'}$ are the same as R_1 and R_2 respectively as previously defined, but with the proviso that $R_{1'}$ and $R_{2'}$ cannot both be H. Hal is halogen.

SCHEME 3

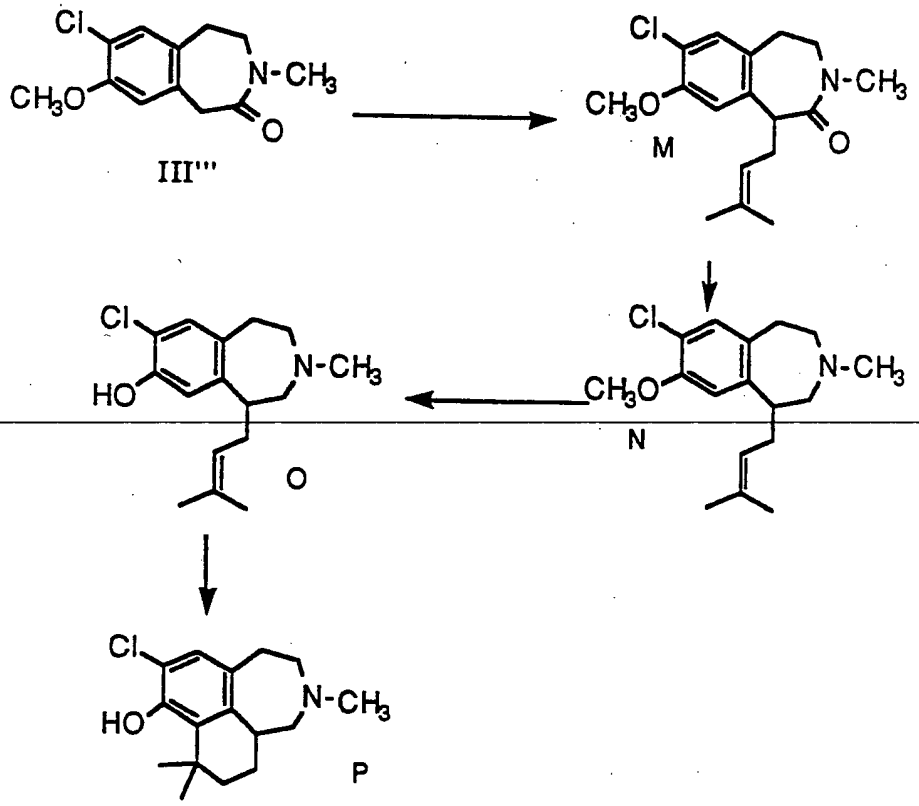


wherein R, hal, Z and Y are as described above, and $R_{1"}$ is C_1-C_4 alkyl or Ar.

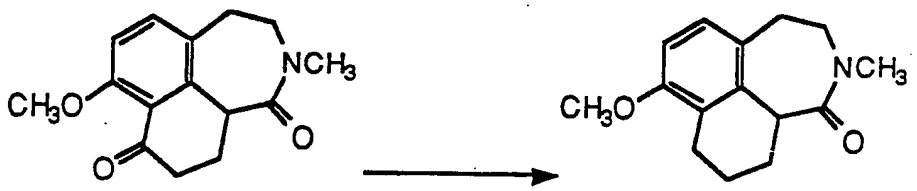
SCHEME 4



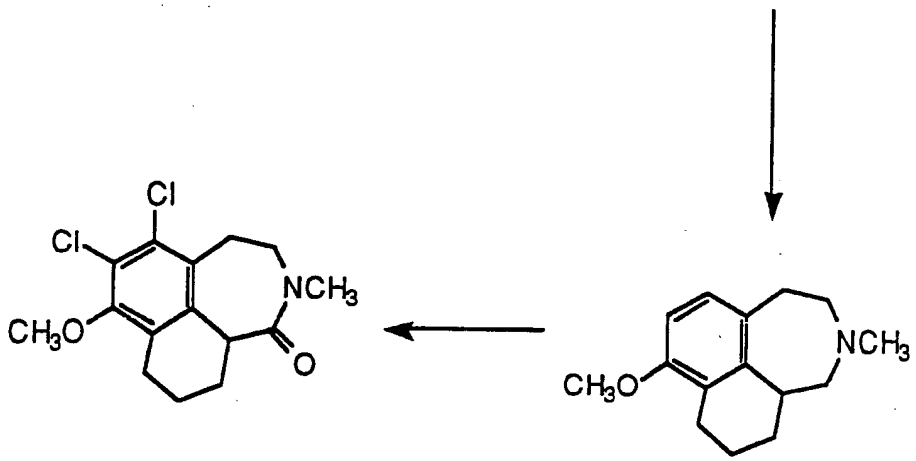
SCHEME 5



SCHEME 6



E' E



G F

Starting materials of formulas III, III', III" or III"', are known, or may be prepared as disclosed in EPA 0285,919 or by methods analogous to those disclosed therein. EPA 0285,919 is herein incorporated by reference.

The compounds of formulas IV, V, and VI are known or can be prepared in accordance with known methods

In Scheme 1, a compound of formula III may be reacted with a compound of formula IV such as methyl acrylate in a very strong base, preferably, sodium hydride. The reaction is carried out in a polar, aprotic, organic solvent such as dimethylsulfoxide (DMSO), tetrahydrofuran (THF), dimethylformamide (DMF), or more preferably a 9:1 mixture of THF and DMF. The temperature of the reaction is not critical. It can be conducted at about room temperature. The product, a compound of formula A', may be isolated by standard techniques such as adjustment of the pH with an acid, like acetic acid, and extraction.

A compound of formula A' may be hydrolyzed to obtain a compound of formula B', by reaction with a mild base such as Na_2CO_3, Li_2CO_3, or more preferably potassium carbonate, in a polar, protic, organic solvent such as ethanol, isopropanol or more preferably a mixture of water and methanol, at about steam bath temperature. The resulting carboxylic acid of formula B' may be isolated by conventional means such as crystallization.

The resulting carboxylic acid may be isolated and then cyclized to obtain a compound of formula C' by treatment with polyphosphoric acid (PPA) at a temperature of about 72-80°, preferably about 80°, for about 1/2 to about 3 hours. The solvent employed for the reaction can be the PPA.

A compound of formula C' may be reduced, by reaction with a reducing agent such as lithium aluminum hydride (LAH), or more preferably BH_3 in an organic solvent such as ether, diglyme or more preferably THF. The reaction may be conducted at the reflux temperature of the solvent employed. The reaction may be carried out for a period of about 1/2 to about 4 hours. Isolation of a compound of formula D' may be conventional means.

In Scheme 2, a compound of formula M' may be prepared by reacting a compound of formula III' with a halogenated olefin of formula V in the presence of a strong base such as lithium diisopropylamide (LDA), or more preferably NaH, in a polar organic solvent such as DMSO, or more preferably a mixture of DME and DMF. The reaction is conducted at a temperature in the range of about -78° to

about 30°, preferably at about room temperature. The resulting compound of formula M' may b_ isolated by conventional techniques such as crystallization.

A compound of formula M' may be reduced to obtain a compound of formula N', by treatment with a reducing agent such as LAH, in a dry, polar, organic solvent, like diethyl ether, or more preferably THF, at temperature starting at about 50° with gradual, cooling to about 40°. The resulting reduced compound of formula N' may be isolated by conventional means such as column chromatography.

A compound of formula N' may be converted to the corresponding hydroxy compound of formula O' by treatment with a strong base such as KH, or more preferably NaH, and a mercaptan, such as butyl-SH, or more preferably ethanethiol in a polar, aprotic organic solvent such as DMSO, or more preferably DMF, under an inert atmosphere such as argon or more preferably nitrogen, at a temperature of from about 100° to about 150° for about 2 hours to about 5 hours. The resulting compound of formula O' may be isolated by conventional means.

A compound of formula O' may be cyclized to a compound of formula P' by treatment with an organic acid, such as CF_3CO_2H, paratoluene sulfonic acid, or more preferably CH_3SO_3H at a temperature of from about 0 to 50° for about 2 hours. The resulting cyclized compound of formula P' may be isolated by conventional techniques such as neutralization of the resulting reaction mixture followed by recrystallization.

In an analogous manner, in Scheme 3, a compound of formula III", by reaction with a compound of formula VI, may be converted sequentially to compounds of formulas M", N", O" and Q".

According to Scheme 4, the compound of formula F is converted to the corresponding hydroxy compound of formula J by treatment with a mineral acid such as HI, HCl or more preferably HBr, in a solvent such as ethanol, acetic acid, or more preferably neat, at a temperature of about 100 to about 150°. The resulting compound of formula J may be isolated by conventional means.

The compound of formula J may be converted to the compound of formula K by treatment with formaldehyde, in the presence of a base such as NaOH, or more preferably potassium hydroxide in an organic solvent such as diglyme, or dimethoxyethane (DME), at a temperature in the range of about 80° to about 100°. The resulting compound of formula K may be isolated by conventional means.

The compound of formula K may be hydrogenated by reaction under hydrogen at a pressure of about 1 to about 5 atmospheres (atm), preferably about 3 atm, in a polar, protic, acidic, organic solvent such as glacial acetic acid, in the presence of a mineral acid such as HCl, H_2SO_4, or more preferably p-toluenesulfonic acid monohydrate, and further in the presence of a hydrogenation catalyst such as Raney nickel, Raney cobalt or more preferably, 20% $Pd(OH)_2$ on carbon. The resulting compound of formula L may be isolated by conventional means such as column chromatography.

The conversion of the compound of formula III''' in Scheme 5, into compounds M, N, O and finally P is described in the examples below.

A compound of formula I or II may be converted to its corresponding acid addition salt, such as its hydrochloride salt, by treatment with HCl. Typically, a compound of formula I or II will be dissolved in a polar organic solvent, such as methanol, or more preferably a mixture of CH_2Cl_2 and EtOH. To this solution will be ethereal HCl, and the resulting hydrochloride salt will be recovered by recrystallization and drying.

According to Scheme 6, the compound of formula E' may be hydrogenated by treatment under about 1 to about 5 atmospheres of hydrogen, for about 1 to about 24 hours in a polar, protic organic solvent such as methanol, isopropanol, or more preferably ethanol, in the presence of a catalyst such as Raney nickel, Raney cobalt, or, more preferably, 10% Pd on carbon. The resulting compound of formula E may be isolated by conventional techniques.

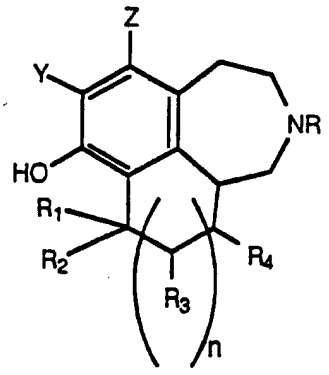
The compound of formula E may be further reduced to obtain the compound of formula F by treatment with a reducing agent such as LAH, or more preferably BH_3, in an aprotic, organic solvent, such as diglyme, diethyl ether, or more preferably THF. The reaction is

carried out by adding, for example, BH_3 in THF, with cooling. After this addition is complete, the resulting mixture is heated at reflux for a period of about 1 to about 4 hours, preferably about 2 hours. The resulting compound of formula F may be isolated by conventional means.

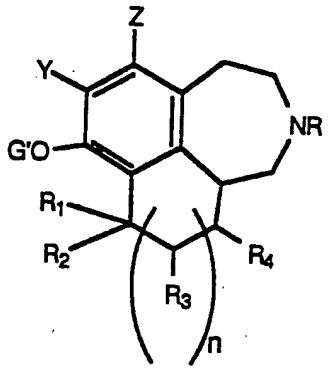
The compound of formula F may be dichlorinated so as to obtain the compound of formula G by treatment with a chlorinating agent such as Cl_2/acetic acid or more preferably SO_2Cl_2 in a molar amount of 3:1 (SO_2Cl_2:substrate) and in a polar, aprotic, organic solvent such as $CHCl_3$, or more preferably CH_2Cl_2 at a temperature in the range of about 0 to about 60°. The resulting dichlorinated compound of formula G may be isolated by neutralizing the resulting reaction mixture, followed by separation by conventional techniques such as column chromatography.

The methoxy compound of formula G may be converted to the corresponding hydroxy compound of formula H in example 2(H) by treatment with a strong acid such as HI or HCl, or, more preferably HBr in a protic, organic solvent such as acetic acid, propionic acid, or more preferably ethanol at temperature in the range of about 100 to about 150° or more preferably about 120° to about 140°. The resulting compound of formula H may be isolated by conventional techniques such as neutralization of the resulting reaction mixture followed by filtration, extraction, and recrystallization.

A compound of formula I' below may be converted to a compound of formula I" below by conventional means.



I'



I''

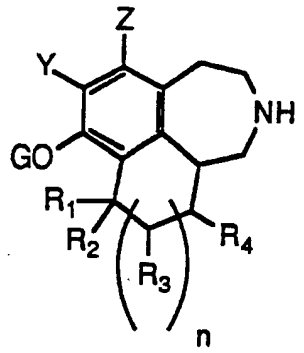
wherein R, R_1, R_2, R_3, R_4, Z, Y, and n are as described above; and G' corresponds to G with the proviso that it cannot be H.

The reaction is carried out by treating a compound of formula I' with an appropriate isocyanate so as the achieve a compound of formula I" with the desired group G'. Isocyanates required to cover the full range of values for G' are either known or can be prepared by known means.

For example, the compound of formula D from example 2(I) may be converted to the compound of formula D" from example 2(I) by reaction with 4-isopropylphenyl isocyanate in an aprotic, organic solvent such as CH_2Cl_2, $CHCl_3$ or more preferably toluene, at the reflux temperature of the solvent employed for a period of about 1/2 to about 3 hours followed by cooling to room temperature. The resulting product may be isolated by conventional techniques such as evaporation of the reaction mixture followed by trituration and drying. This reaction is described more specifically in Example 2(I) below.

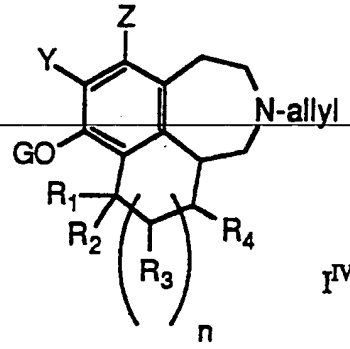
The compounds of formula D', P', Q", and P which are compounds of formula I' may be similarly converted to compounds of formula I" of the invention. Indeed, as noted above, any compound of formula I' may be converted to a corresponding compound of formula I". It will be appreciated that compounds of formulas I' and II" are encompassed by formula I of the invention.

A compound of formula I'",



I'''

wherein R_1, R_2, R_3, R_4, G, Y, Z and n are as described above, may be converted to a corresponding N-allyl compound of formula



I^{IV}

by conventional means such as treatment with an allyl bromide compound. It will be appreciated that a compound of formula D' above, wherein R' is H may be similarly converted to a corresponding N-allyl compound. Compounds of formulas I''', I^{IV}, D' and N-allyl compounds corresponding to compounds of formula D' are encompassed by formula I of the invention.

The compounds of formula I or II of the invention are useful as agents for treating psychoses, drug dependence, D1 dependent neurological disorders, and for providing analgesia.

The antipsychotic activity of the compounds of the invention may be demonstrated in the following protocol.

CONDITIONED AVOIDANCE SUPPRESSION IN RATS

Clinically active antipsychotic drugs are known to depress discrete trial avoidance behavior at doses that do not retard escape response (Ann. N.Y. Acad. Sci. 66, 740 (1957)). A series of experiments

was carried out to assess the ability of the compounds of this invention to suppress the conditioned avoidance response (CAR) in rats.

MATERIALS AND METHODS

Rats were required to jump onto a platform located 6.75 inches (17.15 cm) above the grid floor of an experimental chamber in response to a 5-second tone to avoid a 10-second foot shock (0.6 mA). Each experimental session consisted of 20 such trials presented at 30-second intervals. A correct CAR is scored whenever the rat jumps onto the platform during the tone (prior to foot shock). An escape response is scored when the rat jumps onto the platform during a shock. A response failure is defined as the lack of an escape response during the 10-second shock period.

Groups of 6-8 rats were trained in two consecutive days (total of 40 trials). By day 2, rats that achieved correct CARs on 16 or more of the 20 trials were treated with either a test drug or vehicle on day 3. Suppression of CAR was analyzed statistically using the Student's t-test comparing the performances of drug-treated to vehicle-treated rats. The minimal effective dose (MED) for each drug is defined as the lowest dose tested that significantly ($P \leq 0.05$) reduced avoidance responding.

COMPETITIVE INHIBITION ASSAY

Many compounds capable of effecting reproducible physiological changes in neural tissues are believed to operate by binding at one or more receptor sites. Compounds which interact strongly with these receptor sites in in vitro tests, using homogenates of the target organ or structure, are expected to exhibit similar properties when administered in vivo and are, therefore, therapeutic and/or diagnostic agents.

Binding of a compound to a receptor site, in vitro, is demonstrated by the specificity of binding and the saturability of the available sites. A methodology for characterization of D-1 and D-2

receptor binding and an interpretation of the data are described by Billard et al., Life Sciences 35, 1885 (1984) in which the binding of the benzazepine (R)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepin-7-ol hemimaleate, Compound B* to the dopamine D-1 receptor is characterized. A selectivity for D-1 receptor binding as compared to D-2 receptor binding is believed to confer the therapeutic advantage of avoiding troublesome and potentially irreversible neurological side effects associated with D-2 receptor occupancy.

MATERIALS AND METHODS

Tritiated compound B* and tritiated spiperone (a potent D-2 receptor ligand) are obtained as described in the Billard et al. reference supra and serially diluted in 0.05 M Tris buffer, pH 7.4, as required. Compounds of this invention are synthesized as disclosed herein and diluted in 0.05 M Tris buffer, pH 7.4, as required.

TISSUE PREPARATION

Male Sprague-Dawley rats (200 to 250 g) from Charles River Breeding Laboratories, Mass. are used to obtain brain tissue. The rats are humanely sacrificed and their brains removed and placed on ice. Striatal tissue is excised, pooled, and homogenized (Brinkman Polytron, 10 sec) in 100 volumes (w/v) of ice cold 50 mM Tris buffer, pH 7.4 (at 25°C). The homogenate is centrifuged at 20,000 xg for 10 min. The resultant pellet is rehomogenized in Tris buffer and centrifuged again. The final pellet is resuspended in 50 mM Tris buffer pH 7.4 containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$.

ASSAY

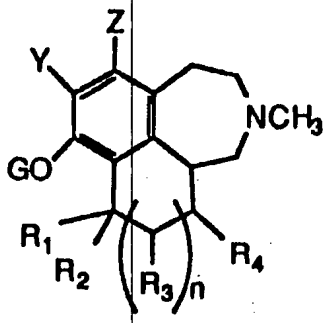
Polypropylene incubation tubes receive 100 µl of the individual test compounds at various concentrations dissolved or suspended in 0.05 M Tris, pH 7.4 containing 4 mg/ml methylcellulose, 100 µl of a solution of tritiated compound B* in Tris buffer (final reaction mixture concentration =0.3 nM) or 100 µl of a solution of ^{3}H-spiperone in

Tris buffer (final concentration =0.2 nM) and 800 µl of tissue suspension (ca. 3 mg/assay). Tubes are incubated at 37°C for 15 minutes and rapidly vacuum filtered through Whatman GF/B filters and rinsed 4 times with 4 ml of ice cold 50 mM Tris buffer, pH 7.4. The filters are transferred to scintillation vials, equilibrated with 10 ml of scintillant (Scintosol, Isolab, Inc.) for 16 hours at 25°C and the radioactivity determined in a liquid scintillation counter. K_i values are determined as described by Billard et al. using the relationship $K_i=IC_{50}/(1 + ([L]/K_D))$ wherein IC_{50}=concentration of test drug necessary to displace 50% of specifically bound tritiated compound B^*, [L]=concentration of radioligand used in the assay, and K_D=dissociation constant. Ki values for the displacement of compound B^*, and Ki values for the displacement of spiperone were determined and are shown in Table I below. The unit for such Ki values is nanomolar (nM).

RESULTS

The inhibition constants (Ki) determined from the assays for a series of compounds of the invention are as shown in Table 1 below.

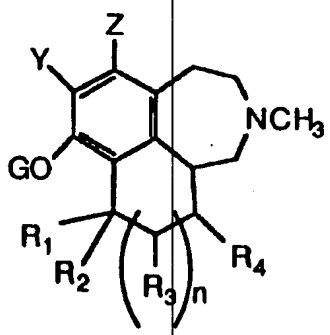
Table 1 - Biological Activity of Compounds of Formula I



Y	Z	n	Q	R_1	R_2	R_3	R_4	K_i Compound B* Displacement	K_i Spiperone Displacement	Rat CAR MED* Oral	Rat CAR MED* sc	mp HCl
Cl	H	1	H	H	H	H	H	6.2	500	>30	0.3	>250
Cl	H	1	Me2NCO	H	H	H	H	1006	8009	10	3	236-9
Cl	H	1	H	C6H5	H	H	H	2080	42800	>30	>10	223-5[a]
Cl	H	1	H	CH3	CH3	H	H	256	218	<30	>10	217-9[a]
Cl	H	1	H	HO	H	H	H	110	6593			153-4
Cl	H	0	H	CH3	CH3	H	H	65	147	≈30	3.0	162-4[a]
Cl	H	1	H	CH3	H	H	H	42	246	3	0.1	194-6[a]
Cl	H	1	H	H	CH3	H	H	51	389			179-81[a]
CH	H	1	H	H	H	H	H	350	3350			265-70
CH3	H	1	H	H	H	H	H	37	1300	≤30		275-280
Cl	Cl	1	H	H	H	H	H	1.1	230	10		275-8
Cl	H	1	4-I-PrPhNHCO	H	H	H	H	51	680	≤30		152-3

* KI Compound B* displacement is described above.
KI Spiperone displacement is described above. nM is nanomolar.
Rat Car MED=minimal effective dose in rats in the conditioned avoidance response suppression test at 1 hr. post-treatment after oral and 0.5 hr. after subcutaneous (sc) administration,
mp HCl means melting point in degrees Celsius of the hydrocholoride salt.
a is free base

Table 1 ctd.



Y	Z	n	G	R_1	R_2	R_3	R_4	K_i Compound B* Displacement	K_i Spiperone Displacement	Rat CAR MED* Oral	Rat CAR MED* sc	mp HCl
Cl	H	1	3,5-(MeO)2Ph-NHCO	H	H	H	H	6.6	405	10		214-6
H	H	1	4-iPrPhNHCO	CH3	H	H	H	134	420	>30		175-8
H	H	1	3,5-(MeO)2Ph-NHCO	CH3	H	H	H	35	337	>30		199-201
Cl	H	1	H	H	—	CH3	—	32	264	>30		154-6
Cl	H	1	H	H	H	CH3 A/B 2:1	H	4.5	250			132-7[a]
Cl	H	1	H	H	H	H	CH_3					270-3

* Where R_2 and R_4 are both ------ there is a carbon-carbon bond.

The comparatively small K_i values of the compounds of the invention in the competitive binding assay with compound B* indicate that the compounds of formula I bind strongly to the D-1 receptor site. The relatively high K_i values for the D-2 site, for which spiperone is highly selective, indicate that the compounds are not specifically bound to that receptor site.

Selective activity for D1 receptors is indicative of these compounds' potential use as D1 antagonists in treating disorders that may be lessened by D1 antagonists as discussed in Beaulieu, Canadian J. Neur. Sci. 14(3):402 (1987) and Waddington, Gen. Pharmac. 19(1):55 (1988). These disorders include disorders associated with stereotypic behaviors and drug dependence. D1 antagonists have been shown to block cocaine- and morphine-dependent pleasure sensations making the compounds of the present invention useful in treating drug dependence. Furthermore, although the precise mechanisms involved in a variety of movement disorders are unknown, it is generally accepted that they all use the striatum as a final common pathway. The striatum contains the highest density of D1 receptors suggesting that movement disorders may be treated using D1 antagonists. Consequently, the compounds of the present invention have potential utility in treating movement disorders such as Parkinson's disease, Huntington's chorea and tardive dyskinesias. Additionally, D1 antagonists have potential utility as inhibitors of disorders associated with repetitive, stereotypic behavior such as Lesch-Nyhan disease.

The antidepressive method of the invention may be demonstrated, for example, by test procedures which measure a compound's effect on tetrabenazine (TBZ)-induced ptosis in mice or which measure a compound's effect on muricide activity in rats as discussed below.

ANTIDEPRESSANT POTENTIAL

EFFECTS ON TETRABENAZINE (TBZ)-INDUCED PTOSIS IN MICE

Clinically active antidepressant drugs are known to block TBZ-induced ptosis in mice (Psychosomatic Medicine, Nodine and Moyer, Eds., Lea and Febiger, Philadelphia, 1962, pp 683-90). Activity in this test is used to predict anti-depressant activity in man.

METHODS AND MATERIALS

Groups of 5 mice are administered test drugs followed 30 minutes later by intraperitoneal (ip) injection of tetra-benazine, 30 mg/kg. Thirty minutes later, the degree of ptosis is evaluated. Percent blockade of each treated group is used to determine ED_{50}'s defined as that dose which prevents ptosis in 50% of mice. ED_{50}'s and 95% confidence limits are calculated by probit analysis.

EFFECTS ON MURICIDAL BEHAVIOR IN RATS

Blockade of muricidal (mouse-killing) behavior in rats is used as a measure of evaluating the anti-depressant activity of drugs (Int. J. Neuro-pharmacol., 5, 405-11 (1966)).

METHODS AND MATERIALS

Groups of 5 rats are administered test drug intraperitoneally and are tested 30 and 60 minutes later for presence of muricidal behavior. Percent blockade of each treated group using data obtained at both these time points is calculated and dose-response data are used to determine each ED_{50}. ED_{50} is defined as that dose which blocks muricide behavior in 50% of treated rats and is calculated using probit analysis.

The analgesic effect of the compounds of formula I and the method for providing analgesia may be xemplified by the Acetic Acid Writhing Test in mice described below.

ACETIC ACID WRITHING TEST IN MICE

The blockade of writhing induced by the intraperitoneal injection of acetic acid is an established experimental animal model for the screening of antinociceptive drugs (drugs which prevent the appreciation or transmission of pain sensations). See Hendershot et al., J. Pharmacol. Exp. Therap. 125:237, (1959) and Koster et al., Fed. Proc. 18:412, (1959).

METHODS AND MATERIALS

Compounds to be tested are dissolved or suspended in aqueous 0.4% methylcellulose vehicle. For oral administration, dosages are prepared for delivery of the selected weight of compound in a total volume of 20 mg/kg of body weight. For subcutaneous or intraperitoneal administration, dosages are prepared for delivery of the selected weight of compound in a volume of 10 ml/kg of body weight.

The test procedure is that described by Hendershot et al., supra, except that acetic acid is substituted for phenylquinone. Groups of five male CF1 mice (20-26 g.) are dosed orally with test drug and injected 15 minutes later with 0.6 ml aqueous acetic acid (10 mg/kg). The mice are placed in a large observation beaker and the number of writhes for each animal is counted during a 10 minute interval starting 3 minutes after injection of acetic acid. A writhe is defined as a sequence of arching of the back, pelvic rotation and hindlimb extension. Initial screening is performed using a dosage of 30 mg/kg. If this dose affords 50% or greater reduction in the number of writhes compared to the control, the animal is considered to be protected, a dose response curve is developed using a logarithmic sequence of lower doses and an ED_{50} is determined by interpolation.

The compounds of the invention are selective D1 receptor antagonists. D1 antagonists have been shown to block cocaine- and morphine-dependent pleasure sensations making the compounds of the present invention useful in treating drug dependence. The activity of the compounds of the invention in treating drug dependence may be

demonstrated by the protocol described in Kleven, et al., Psychopharmacology (1988) 95: pp. 427-429 or by the procedure described in Koob, et al., Neuroscience Letters, 79 (1987) pp. 315-320.

The compounds can be administered orally, topically, parenterally, or by oral or intranasal inhalation. The preferred mode of administration is orally or intravenously.

The compounds can be administered in conventional oral dosage forms such as capsules, tablets, pills, powders, suspensions or solutions prepared with conventional pharmaceutically acceptable excipients and additives, using conventional techniques. Parenteral preparations, i.e., sterile solutions or suspensions are also made by conventional means. Inhalation administration can be in the form of a nasal or oral spray. Insufflation is also contemplated.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may comprise from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparation may also include solutions for intranasal administration.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions. These particular solid form preparations are most conveniently provided in unit dose form and as such are used to provide a single liquid dosage unit. Alternatively, sufficient solid may be provided so that after conversion to liquid form, multiple individual liquid doses may be obtained by measuring predetermined volumes of th liquid form preparation as with a syringe,

teaspoon or other volumetric container. When multiple liquid doses are so prepared, it is preferred to maintain the unused portion of said liquid doses at low temperature (i.e., under refrigeration) in order to retard possible decomposition. The solid form preparations intended to be converted to liquid form may contain in addition to the active material, flavorants, colorants, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents and the like. The solvent utilized for preparing the liquid form preparation may be water, isotonic water, ethanol, glycerine, propylene glycol and the like as well as mixtures thereof. Naturally, the solvent utilized will be chosen with regard to the route of administration, for example, liquid preparations containing large amounts of ethanol are not suitable for parenteral use.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

For preparing suppositories, a low melting wax such as mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into conveniently sized molds, allowed to cool and thereby solidify.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

When used orally, the compounds of the invention can be administered to a mammal in need of such treatment in an amount ranging from about 0.01 mg/kg body weight to about 30.0 mg/kg body weight. When used parenterally, the compounds of the invention can be administered in a range of about preferably from about 0.001 mg/kg body weight to about 10.0 mg/kg body weight per day.

Determination of the proper dosage of a compound of the invention for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages that are less than the

optimum dose of the compound, Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

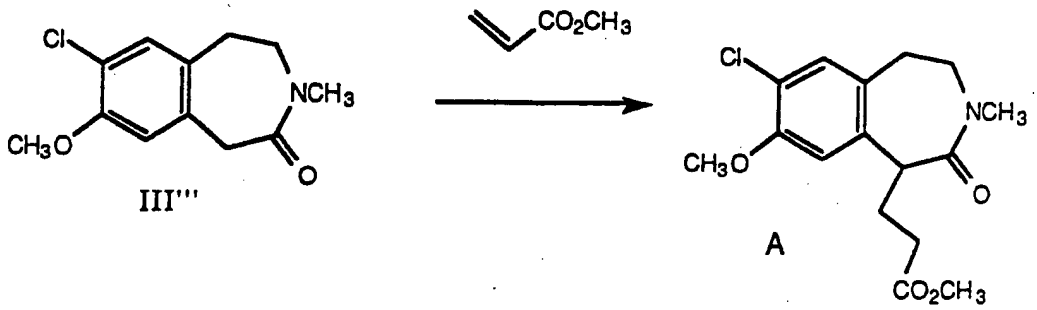
The amount and frequency of administration of the compounds of formula I and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptom being treated.

The invention disclosed herein is exemplified by the following preparative examples, which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

Example 1

Preparation of 6-Chloro-2-Methyl-1,2,3,4,8,9,10,10a-octahydro-naphth [1,8-cd]azepin-7-ol.

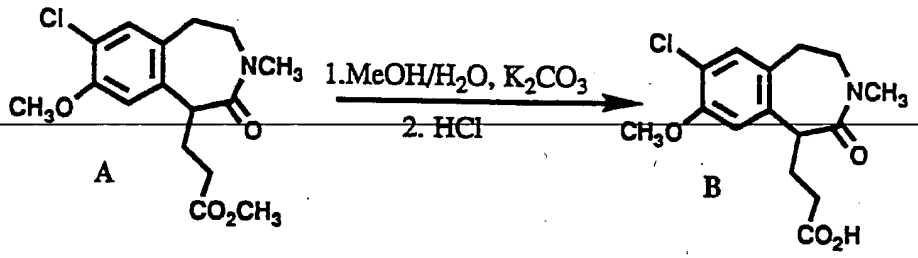
A. 3-(7-chloro-8-methoxy-3-methyl-2-oxo-2,3,4,5-tetrahydro-1H-3-benzazepin-1-yl)propionic acid, methyl ester.



A 60% suspension of NaH in mineral oil (0.06 mole) was added portionwise with cooling and stirring to a solution of the starting material III''' (14.4 g, 0.06 mole) in 120 ml of a 9:1 mixture of tetrahydrofuran (THF)/dimethylformamide (DMF). The resulting mixture was stirred for 20 minutes, and a solution of methyl acrylate (0.06 mole)

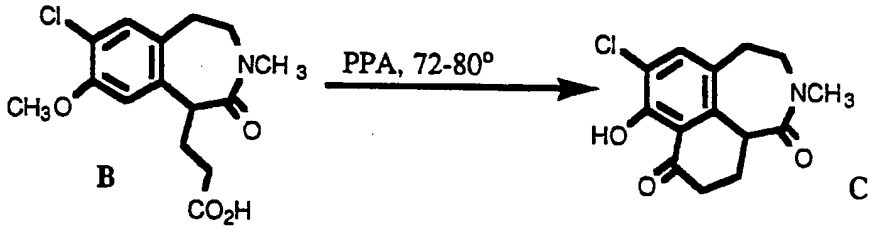
in 10 ml of THF added dropwise with stirring. After stirring for an additional 2 hrs, 15 ml of water was added dropwise with cooling and stirring. After frothing had subsided, the reaction mixture was diluted with 350 ml of water, and the pH adjusted to ~ 5 with acetic acid. The mixture was extracted with 200 ml of ether followed by 100 ml of methylene chloride. The combined extracts were dried over $MgSO_4$, and evaporated in vacuo. The residue was triturated with cold ether, and the solid product filtered and dried to give 7.95 g of product, mp 95-97°.

B. 3-(7-chloro-8-methoxy-3-methyl-2-oxo-2,3,4,5-tetrahydro-1H-3-benzazepin-1-yl)propionic acid.



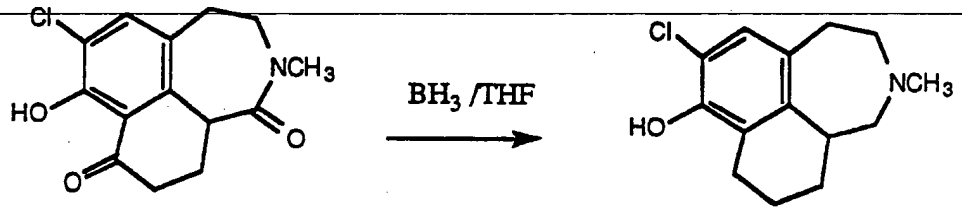
A mixture of 15.0 g of K_2CO_3, 80 ml of water, 120 ml of methanol, and 7.95 g of product A above was heated on the steambath for 2 hrs. The resulting mixture was the concentrated to ca. 100 ml, diluted with 150 ml of water, chilled, and extracted with 100 ml of ether. The aqueous layer was separated, cooled, and acidified with concentrated HCl. The precipitated solids were filtered off, washed with water, and allowed to dry in air overnight to give 7.25 g of product.

C. 6-Chloro-1,8-diketo-2-Methyl-1,2,3,4,8,9,10,10a-octahydro-naphth[1,8-cd]azepin-7-ol.



A mixture of 6.75 g of the preceding product B in 70 g of polyphosphoric acid was heated in an oil bath at 72-80° with stirring for 45 min. The mixture was then poured over 600 ml of ice-water with stirring. After 15 minutes of stirring, the mixture was extracted with two 100 ml portions of methylene chloride. The combined extracts were filtered through Celite, then dried over $MgSO_4$. After filtration of the drying agent, the filtrate was evaporated to dryness to give a viscous syrup which was crystallized from 20 ml of ethyl acetate thus yielding 3.9 g of product C, mp 140-142°.

D. 6-Chloro-2-Methyl-1,2,3,4,8,9,10,10a-octahydro-naphth[1,8-cd]azepin-7-ol.



C D

A solution of 3.9 g of product C above in 20 ml of THF was treated with 50 ml of 1 M BH_3 in THF. The resulting mixture was heated at reflux for 6.5 hrs., then allowed to stand at room temperature overnight. The mixture was concentrated to about, 20 ml, and then treated dropwise with cooling with 20 ml of ethanol followed by 50 ml of 4 N HCl. This mixture was then heated on the steambath with stirring for 30 min, diluted with 100 ml of water, and adjusted to pH~8 by dropwise addition of 50% NaOH. Precipitated material was filtered off, washed with cold water, and air dried overnight yielding 2.6 g of product.

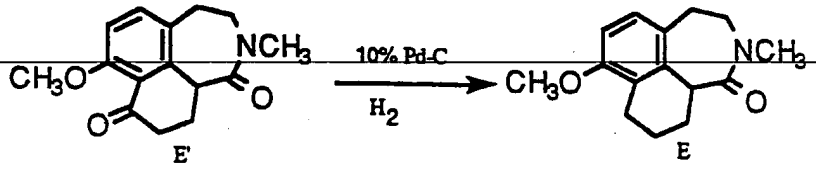
The aqueous filtrates were extracted with 50 ml of CH_2Cl_2, and the extract evaporated to give ca. 300 mg of oily residue. The solid product was recrystallized from 180 ml of CH_3CN/EtOH (1:2) to give 1.85 g of hydrochloride salt of D, mp 277-280°. This material was dissolved in 120 ml of boiling water, the solution treated with solid $NaHCO_3$ to pH~8, the solution chilled, and the precipitated solids filtered giving 1.45 g of free base. This material was chromatographed over 150 g of thin-layer

chromatography grade silica gel eluting with $CHCl_3$/EtOH/NH_4OH (50:3:1). Fractions which were homogeneous by TLC were combined and evaporated, and the residue dried in vacuo at 90 ° for 4 hrs to yield 1.0 g of product D, mp 177-178°.

Example 2

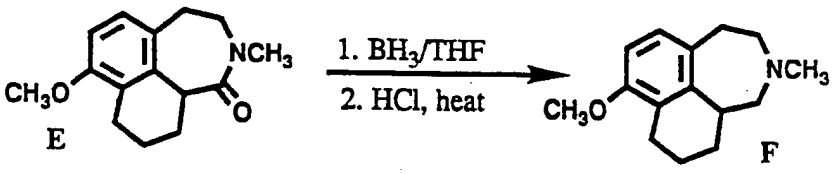
Preparation of 5,6-Dichloro-2-Methyl-1,2,3,4,8,9,10,10a-octahydro-naphth[1,8-cd]azepin-7-ol.

E. 7-Methoxy-2-Methyl-1-Oxo-1,2,3,4,8,9,10,10a-octahydro-naphth[1,8-cd]azepine.



A suspension of 20.0 g of E' in 350 ml of EtOH and 10 ml of conc. HCl was hydrogenated over 2.2 g of 10% Pd on carbon at 20-25 pounds per square inch gage (psig) for 24 hrs. Catalyst was filtered, and solvent evaporated to give 18.0 g of solid product E. Compound E' was prepared in a manner similar to the preparation of compound C in Example 1(C) above.

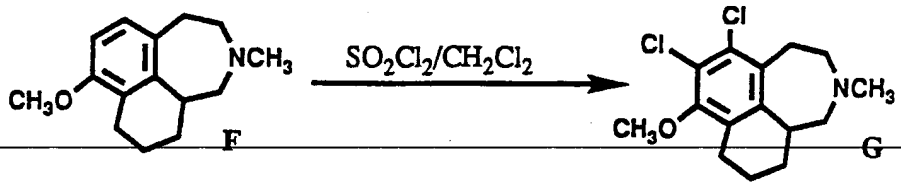
F. 7-Methoxy-2-Methyl-1,2,3,4,8,9,10,10a-octahydro-naphth[1,8-cd]azepine.



A solution of 18.0 g of product E in 200 ml of THF was treated with 145 ml of 1 M BH_3 in THF dropwise with cooling and stirring. The reaction mixture was then heated at reflux with stirring overnight. The resulting mixture was reduced to dryness at slightly reduced pressure, and the residue then treated by dropwise addition of 100 ml of

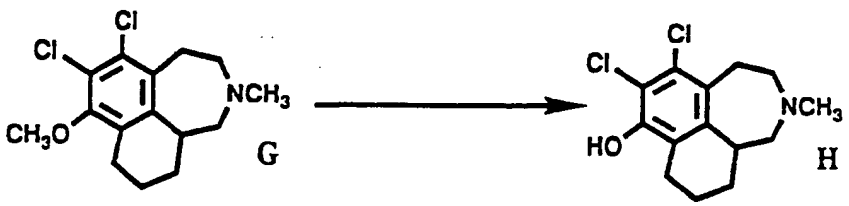
ethanol with cooling and stirring followed by 70 ml of 20% HCl. After heating at reflux for 2 hrs, most of the solvent was removed in vacuo, the residue diluted with 300 ml of water, and the solution rendered basic with 50% NaOH. The resulting mixture was extracted with two 200 ml of ether, the combined extracts dried over $MgSO_4$, filtered, and the filtrate evaporated to dryness to give 15.3 g of product F as a viscous syrup.

G. 5,6-Dichloro-7-Methoxy-2-Methyl-1,2,3,4,8,9,10,10a-octahydro-naphth[1,8-cd]azepine.



A solution of product F (15.0 g) in 300 ml of CH_2Cl_2 was treated by dropwise addition of 160 ml of a 1 M solution of SO_2Cl_2 in CH_2Cl_2 with cooling and stirring in an ice bath. Stirring was continued for 1 hr in the ice bath, then at room temperature overnight. The reaction mixture was then cooled in ice and treated by slow addition of a 5% solution of K_2CO_3 with stirring until pH 8 was reached. The organic layer was then separated, dried over $MgSO_4$, filtered, and evaporated to dryness to give ~19 g of a dark viscous syrup. This material was taken up in 40 ml of CH_2Cl_2 and chromatographed over 600 g of thin layer chromatography (tlc) grade silica gel eluting with CH_2Cl_2/EtOH/NH_4OH (100:3:1). Fractions containing the desired product, as determined by tlc, were combined, and evaporated to dryness giving 2.9 g of viscous syrup G.

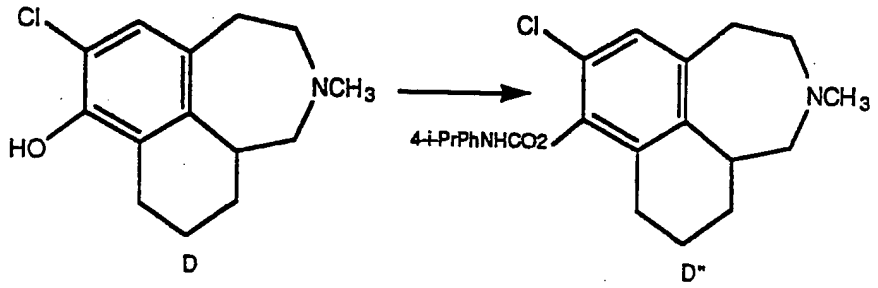
H. 5,6-Dichloro-2-Methyl-1,2,3,4,8,9,10,10a-octahydro-naphth[1,8-cd]azepin-7-ol.



Product G was dissolved in 50 ml of EtOH and filtered to remove a small amount of insoluble material. The filtrate was evaporated to dryness, the residue treated with 30 ml of 48% HBr, and the mixture then stirred and heated in an oil bath at 130° for 6 hrs. The mixture was then reduced to a volume of ~15 ml under reduced pressure, and the residue dissolved in 600 ml of boiling water. The hot mixture was treated portionwise with solid $NaHCO_3$ to pH ~ 8, and allowed to stand at room temperature overnight.

The precipitated dark solids were filtered and washed with water. The filtrates were extracted with 150 ml of CH_2Cl_2 and the extracts and solids combined. The resulting solution was dried over $MgSO_4$, filtered, and treated with excess ethereal HCl. The mixture was then evaporated to dryness, and the residue digested with 60 ml of ethyl acetate/ethanol (3:1) on the steam bath. After cooling, the solids were filtered and dried at 90° in vacuo for 5 hrs to give 2.1 g of product H mp 275-278°.

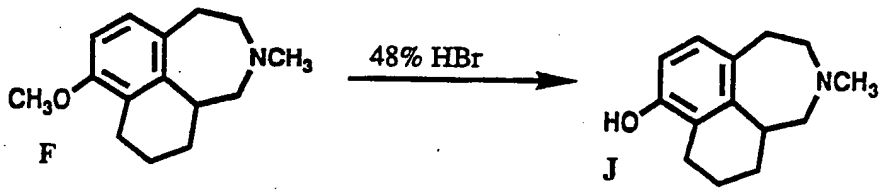
I. Preparation of 6-Chloro-7-[(4-Isopropylphenylamino)-Carbonyloxy]-2-Methyl-1,2,3,4,8,9,10,10a-Octahydro-Naphth[1,8-cd]azepine, hydrochloride.



4-Isopropylphenyl isocyanate (0.33 g, 2.0 mmol) was added to a suspension of compound **D** (0.3 g, 1.2 mmol) in 30 ml of toluene, and the mixture heated at reflux for 4.5 hrs. The reaction mixture was then cooled to room temperature, and stirred overnight under nitrogen. Evaporation of solvent in vacuo left an oil, which was dissolved in ether and treated with ethereal HCl. A small amount of ethanol was added to the suspension, and the mixture evaporated to dryness. The

resulting solid was triturated with acetonitrile, filtered, and dried in vacuo to give 0.49 g of product mp 152-153°.

J. Preparation of 2-Methyl-1,2,3,4,8,9,10,10a-Octahydro-Naphth[1,8-cd]azepine-7-ol.



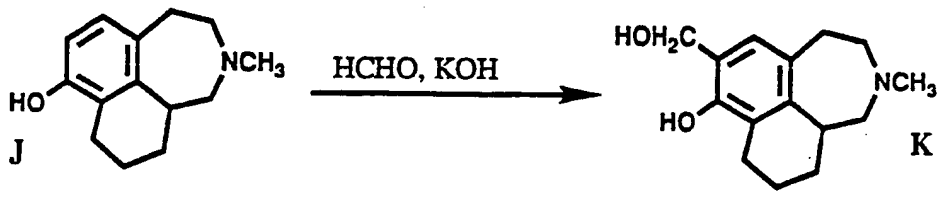
F J

A solution of compound **F** (27 g) in 250 ml of 48% HBr was heated in an oil bath at 125-130° with stirring for 6.5 hrs. The mixture was then chilled in an ice bath, and the precipitated solids filtered and washed with cold water. The wet solids were then dissolved in 75 ml of dimethylformamide (DMF) with heating, and poured into a solution of 30 g of $NaHCO_3$ in 800 ml of water with vigorous stirring. The mixture was cooled in ice for 1 hr, and the precipitated solids filtered, washed with water, and air-dried overnight to give 16.7 g of product J, mp 265-270°.

The acidic filtrates were evaporated almost to dryness under reduced pressure, and the residue dissolved in 30 ml of DMF with heating. The resulting solution was then poured into the preceding $NaHCO_3$ neutralized filtrate with vigorous stirring, and the mixture again chilled in an icebath for one hr. Filtration and air drying of the resulting precipitate furnished an additional 7.0 g of product.

Preparation of 2,6-Dimethyl-1,2,3,4,8,9,10,10a-Octahydro-naphth[1,8-cd]azepine-7-ol.

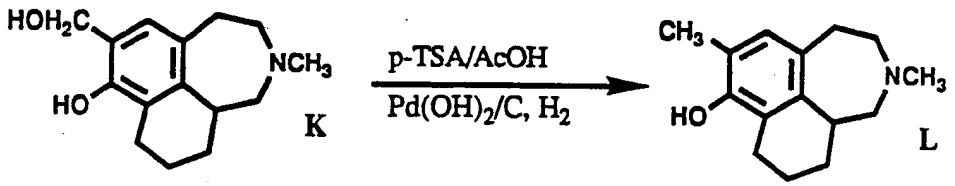
K. 6-Hydroxymethyl-2-Methyl-1,2,3,4,8,9,10,10a-Octahydro-Naphth[1,8-cd]azepine-7-ol.



J K

To a solution of 7.0 g of compound J in 125 ml of dimethoxyethane and 125 ml of 3% KOH was added 9.0 ml of 38% formaldehyde solution. The reaction mixture was heated in an oil bath at 85° with stirring for 40 minutes. It was then cooled to room temperature, and treated dropwise with glacial acetic acid to pH. The mixture was then concentrated to 150 ml, diluted with 100 ml of water, and extracted with two 75 ml portions of methylene chloride. The extracts were combined, dried, and evasporated to dryness. The residue was triturated with a mixture of 1:1 ethanol/acetonitrile and the solids filtered to give 2.2 g of product which was used directly in the next step.

L. 2,6-Dimethyl-1,2,3,4,8,9,10,10a-Octahydro-Naphth[1,8-cd]azepine-7-ol, hydrochloride.

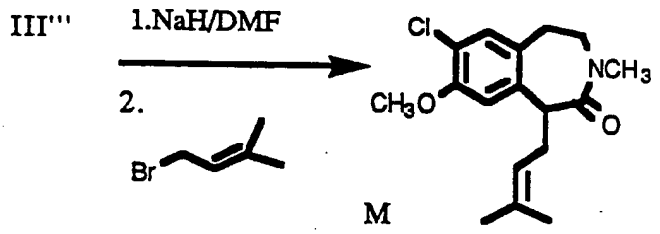


A solution of compound **K** (2.2 g) and p-toluenesulfonic acid ($_p$-TSA) monohydrate (6.0 g) in 85 ml of glacial acetic acid was hydrogenated over 500 mg of 20% $Pd(OH)_2$ on carbon at 60 psig for 6.5 hrs. The catalyst was then filtered off, the filtrate concentrated to 15 ml under reduced pressure, and added in small portions with stirring to 250 ml of saturated $NaHCO_3$ solution. The resulting mixture was then extracted with two 75 ml portions of CH_2Cl_2, and the combined extracts evaporated to dryness to give ca. 2 g of viscous residue. This material was redissolved in ca. 15 ml of CH_2Cl_2/EtOH (8:2), and chromatographed over 50 g of tlc grade silica gel eluting with CH_2Cl_2/EtOH/NH_4OH (50:3:1). Fractions containing the faster-moving component were combined and evaporated to dryness, and the residue digested for a short time with a small amount of CH_3CN. On cooling, the material crystallized. This material was converted to the hydrochloride salt by treatment of a CH_2Cl_2-EtOH solution with ethereal HCl. The crude salt was digested with a 1:1 mixture of EtOAc/EtOH, chilled, and the solid product filtered to give 1.68 g of compound L, mp 275-280° after drying in vacuum at 80° for 3.5 hrs.

Example 3

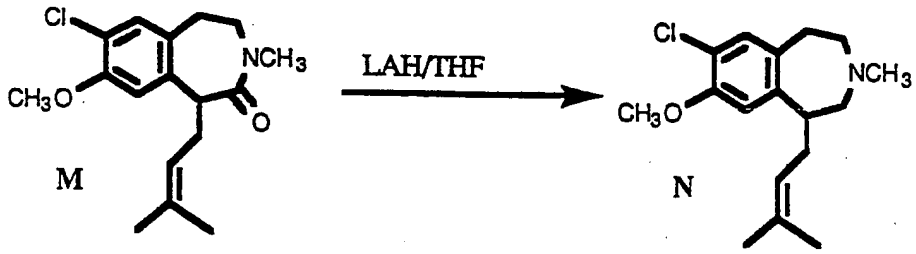
Preparation of 6-Chloro-2,8,8-Trimethyl-1,2,3,4,8,9,10,10a-Octahydro-Naphth[1,8-cd]azepin-7-ol.

M. 6-Chloro-1-(3-methyl-2-butenyl)-2-oxo-3-methyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine.



A suspension of NaH (1.92 g, 60% in mineral oil) was added in small portions to a solution of III'' (4.8 g) in a mixture of 35 ml of 1,2-dimethoxyethane and 15 ml of DMF. After 30 min. a solution of 0.022 mole of prenyl bromide in 10 ml of DMF was added dropwise with stirring. Stirring was continued at 40° for 1.5 hrs, and the reaction mixture then poured into 250 ml of icewater in small portions with vigorous stirring. The precipitated solids were filtered, washed with cold water, and crystallized from acetonitrile to give 2.8 g of product M mp 143-145°.

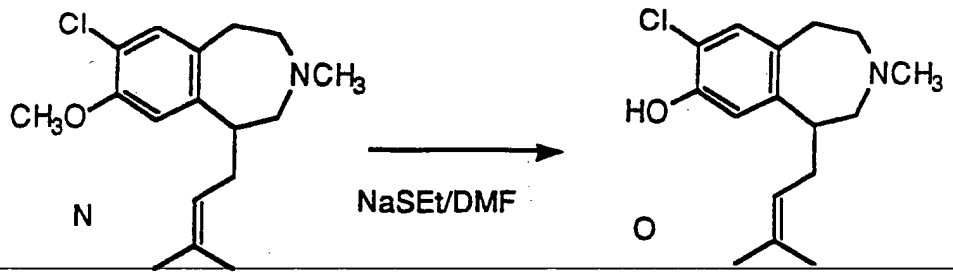
N. 6-Chloro-1-(3-methyl-2-butenyl)-3-methyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine.



A solution of product M (30.5 g) in 350 ml of dry THF was added in a rapid dropwise manner to a stirred suspension of LAH_4 (10 g) in 200 ml of dry THF. The mixture was stirred at 50° for 1 hr, then at 40° for another 1 hr. The cooled and stirred reaction mixture was then treated by the dropwise addition of 10 ml of water, 10ml of 15% NaOH, and finally with another 30 ml of water. The precipitated solids were filtered through Celite, and washed with two 100 ml portions of ether. The combined filtrates were then dried over anhydrous K_2CO_3, filtered, and evaporated to dryness to give about 27 g of viscous residue. This material was chromatographed on a column of 400 g of tlc grade silica gel, initially eluting with CH_2Cl_2/EtOH/NH_4OH (100:3:1), and then with

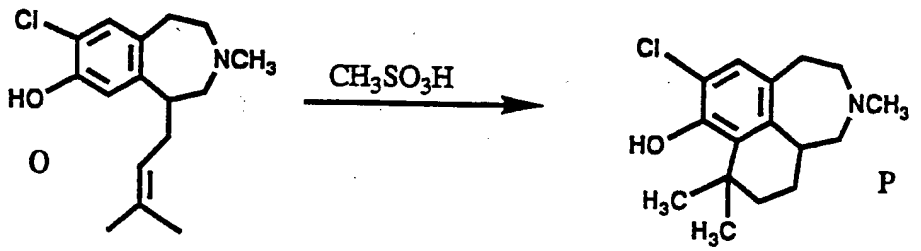
CH_2Cl_2/EtOH/NH_4OH (50:3:1). Fractions containing the slower moving spot on tlc were combined and evaporated in vacuum to give 19.2 g of compound N as a viscous syrup.

O. 6-Chloro-1-(3-methyl-2-butenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol.

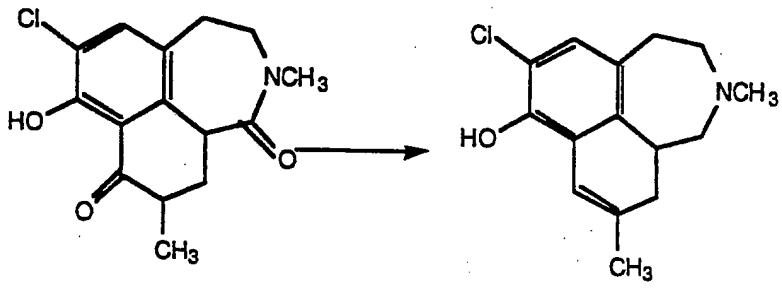


A solution of ethanethiol (12 ml) in 150 ml of DMF was treated portionwise with 7.5 g of 60% NaH dispersion in mineral oil with stirring. A solution of 19.0 g of product N in 30 ml of DMF was added to this mixture dropwise with continued stirring. The mixture was blanketed under nitrogen, stirred, and heated at 115 º for 3 hrs. After cooling the reaction mixture to 50º, it was poured into 1400 ml of ice-water, and the pH adjusted to ~8 by addition of AcOH. The mixture was extracted with two 200 ml portions of CH_2Cl_2, and the combined extracts dried over $MgSO_4$, filtered, and evaporated to dryness to give 18.1 g of viscous syrup. This material was redissolved in 200 ml of CH_2Cl_2, and washed with three 400 ml portions of water. The CH_2Cl_2 layer was redried over $MgSO_4$, and evaporated to give 15.0 g of compound O as a viscous syrup.

P. 6-Chloro-2,8,8-Trimethyl-1,2,3,4,8,9,10,10a-Octahydro-Naphth[1,8-cd]azepin-7-ol.



A solution of 400 mg of compound O in 8 ml of CH_3SO_3H was stirred at room temperature for two hrs, then poured into 100 ml of water and adjusted to pH 8 by addition of NaOH and finally AcOH. After standing at room temperature overnight, the precipitated solids were filtered, washed with water, and recrystallized from acetonitrile/ethanol (1:1). The solid product was filtered and dried at 80° in vacuo for 6 hrs to give 260 mg of product P mp 217-219°.



II

Q. A solution of 9.5g of lactam in 125 ml of dry tetrahydrofuran was added dropwise with cooling and stirring to 100 ml of 1M borane/THF. The mixture was then warmed to room temperature, and heated at reflux overnight. The reaction mixture was evaporated to dryness at 70 degrees under reduced pressure. 40 ml of ethanol was added to the residue, which was then treated with 40 ml of 20% HCl. The mixture was heated on a steambath for 90 minutes, cooled, organic solvents removed at reduced pressure, and the residue diluted with 150 ml of icewater. The mixture was filtered and treated with small portions of sodium bicarbonate to pH 8. It was extracted with methylene chloride,

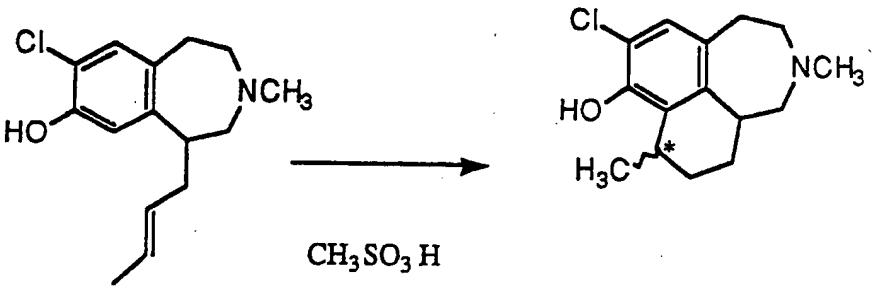
the extracts dried over magnesium sulfate, filtered, and evaporated to dryness to give 6.5 g of product.

This material was chromatographed over 300 g of silica gel eluting with a mixture of methylene chloride/ethanol/water in the ratio of 100:3:1. Fractions found to contain product via thin-layer chromatography were combined, and evaporated to dryness. Trituration of the residue with acetonitrile resulted in the formation of solids, which were recrystallized from acetonitrile to give 2.2 g of solids which were again recrystallized from ethyl acetate to give 1.15 g of material which was rechromatographed on 90 g of silica gel eluting with methylene chloride/ ethanol/ammonium hydroxide 50:3:1. Two products were eluted after evaporation of solvents from appropriate fractions. Treatment of the slower eluting product with hot acetonitrile gave the compound of formula II, mp 154-6.

The starting lactam was obtained by procedures analogous to those of example 1(C) above.

Example 4

Preparation of both isomers of 6-chloro-2,8-dimethyl-1,2,3,4,8,9,10,10a-octahydro-naphth[1,8-c,d]azepin-7-ol



S T

R. 2.5 g of compound S was cooled in an ice-bath and 50 ml of methanesulfonic acid were added dropwise. The mixture was stirred at room temperature for 2 hours, then poured into an ice-cooled solution of 30 g NaOH in 300 ml of water. The pH of the solution was then adjusted to about 6 with 50% NaOH, and then to about 8 with $NaHCO_3$. The precipitated solids were filtered and washed with 200 ml of water, then stirred with 100 ml of CH_2Cl_2 and 300 ml of water to

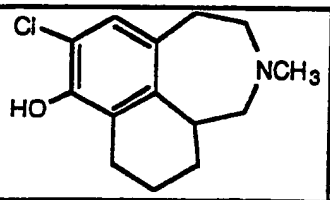
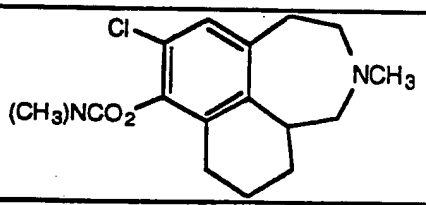
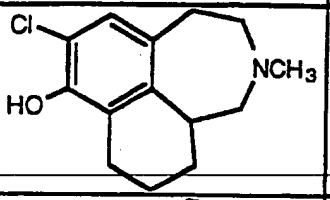
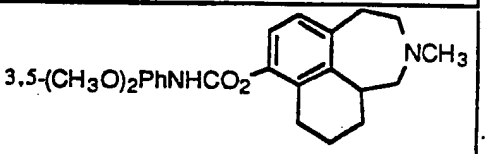
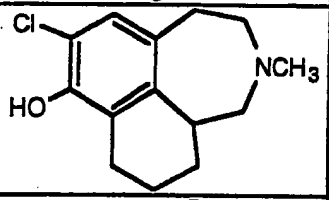
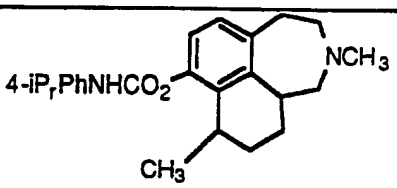
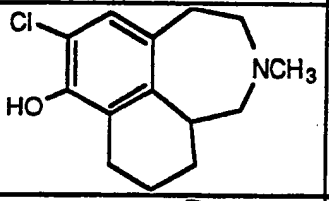
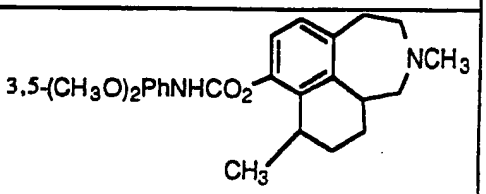
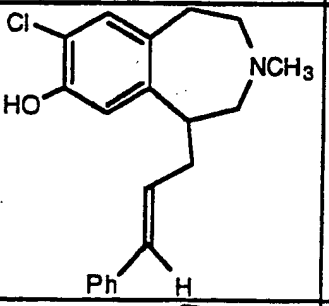
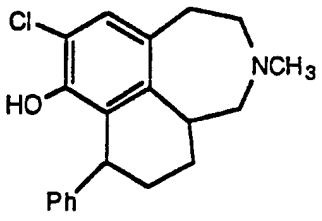
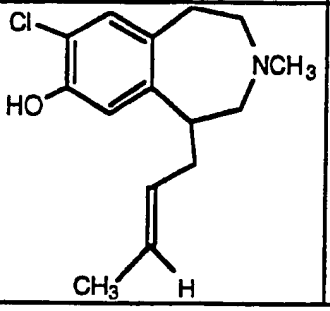
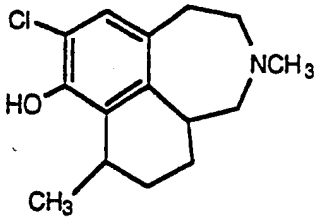
completely dissolv the solids. The wat r layer was separated, and extracted with two 100 ml portions portions of CH_2Cl_2, which were combined with the original extract and dried over $MgSO_4$. The mixture was then filtered, and the filtrate evaporated to give a solid residue.This was dissolved in hot ethyl acetate containing a small amount of ethanol, and cooled in the refrigerator overnight.

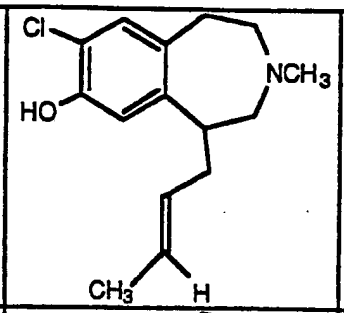
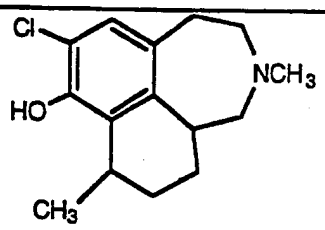
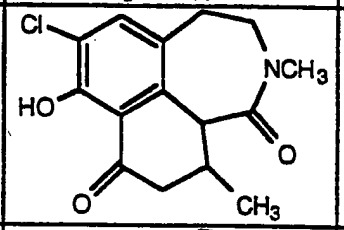
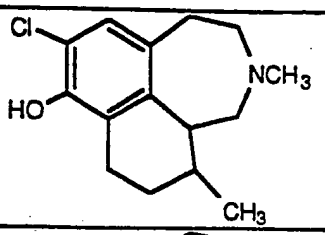
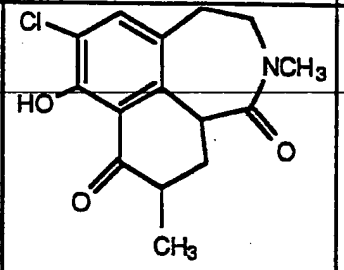
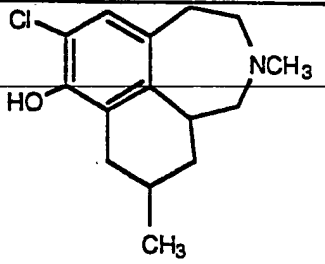
A crystalline product was filtered from the mixture to give one stereoisomer of compound T, mp 194-196°. The filtrate was evaporated to dryness, and the solid residue was collected and washed with a small amount of ethyl acetate.This material was then recrystallized from ethyl acetate containing a small amount of ethanol to give a crystalline product mp 179-181°,which was the other stereoisomer of compound T. These compounds are stereoisomers about the position marked with an *. The absolute stereochemical configuration was not assigned to the two stereoisomers that were separated.

Starting material S was prepared accoording to Scheme 2 in a manner analogous to that described for compound O.

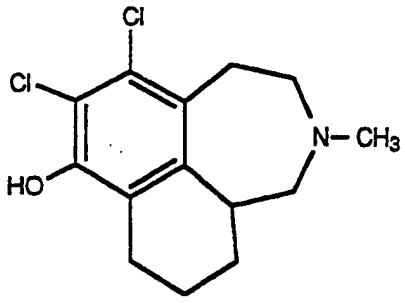
The lefthand column of Table 2 below lists a preparative procedure as described in a particular example. The middle column lists a starting material. The righthand column lists a product. The preparative procedure, starting material, and product in each row of Table 2 below are related. Specifically, by subjecting the listed starting material in a given row to basically the same preparative procedures as are set forth in the listed example of that row, there was obtained the product of that row.

Table 2

Preparative Procedures	Starting material	Product
Example 2(I)		
Example 2(I)		
Example 2(I)		
Example 2(I)		
Example 3 (P)		
Example 3(P)		 isomer A

Example 3(P)		 isomer B
Example 1(D)		
Example 1(D)		 A/B 2:1

The following formulations exemplify some of the dosage forms of the compositions of this invention. In each, the term "active compound" refers to the compound of the formula:



However, this compound may be replaced by equally effective amounts of other compounds of the invention as described above.

EXAMPLE A

Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose NF	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water USP	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate NF	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

EXAMPLE B

Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose NF	103	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	7	7
	Total	250	700

Method of Manufacture

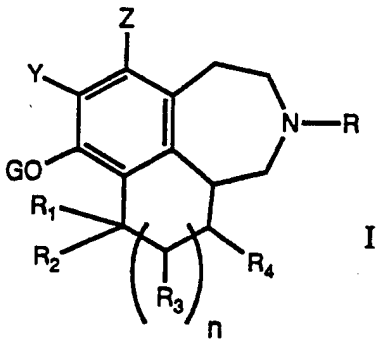
Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

An injectable formulation comprising a compound of the invention may be prepared by using techniques which are conventional in the art.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

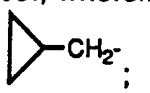
WHAT IS CLAIMED IS:

1. A compound of the structural formula



I

or a pharmaceutically acceptable salt thereof, wherein

R represents H, alkyl, allyl or  ;

n represents 0 or 1;

R_1 and R_2 may be the same or different and each independently represents H, OH, C_1-C_4 alkyl or Ar, with the proviso that R_1 and R_2 may not both be OH, and with the further proviso that when n is 0, R_1 is C_1-C_4 alkyl or Ar, R_2 is CH_3 and R_4 is H;

R_3 and R_4 may be the same or different and each independently represents H or C_1-C_4 alkyl;

G represents H, $(R_5,R_6)NCO$- or ArNHCO-;

R_5 and R_6 may be the same or different and each independently represents H, C_1-C_4 alkyl, or Ar;

Ar represents phenyl or substituted phenyl;

Y and Z may be the same or different and each independently represents H, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, or C_1-C_4 haloalkyl,

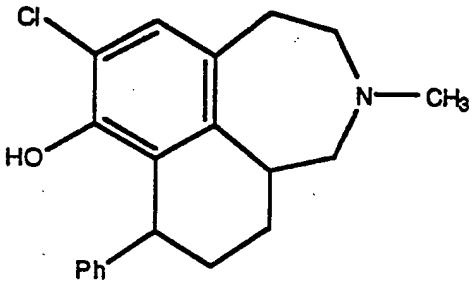
with the proviso that:

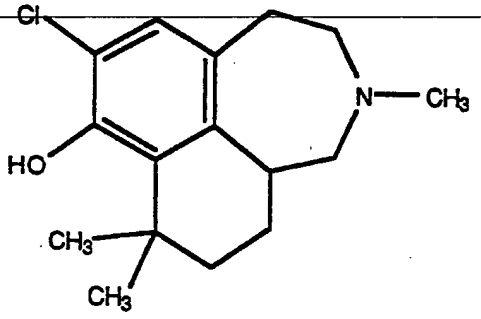
A. At least one of R_1, R_2, R_3 and R_4 must not be hydrogen; and/or

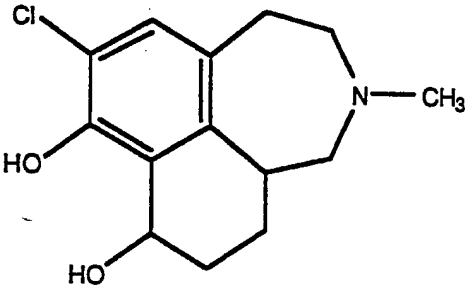
B. G must represent ArNHCO-, or $(R_5, R_6)NCO$- where at least one of R_5, R_6 represents Ar.

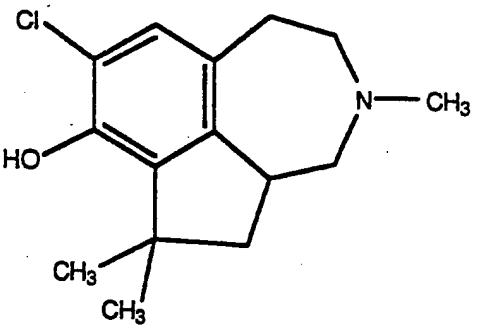
2. A compound according to claim 1, wherein n is 1, R is alkyl, Y and Z are each independently H or Cl, and G is H or ArNHCO-.

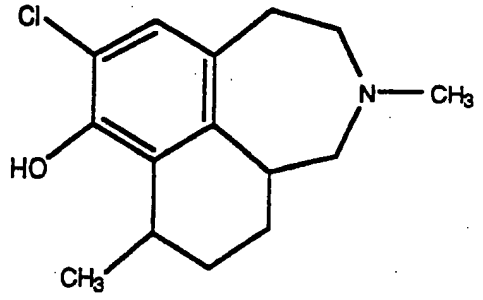
3. A compound according to claim 1, selected from the group consisting of

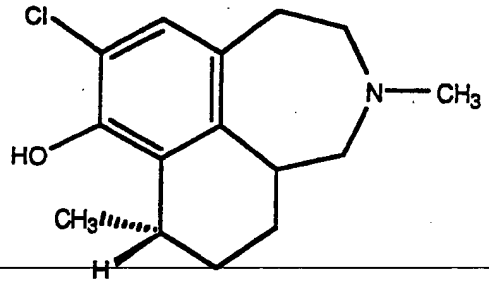


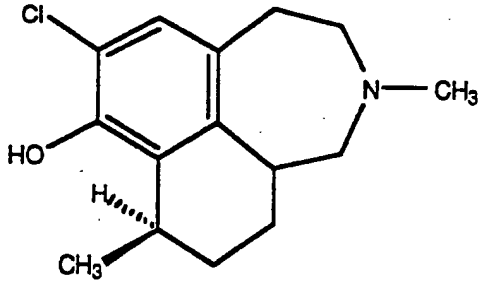


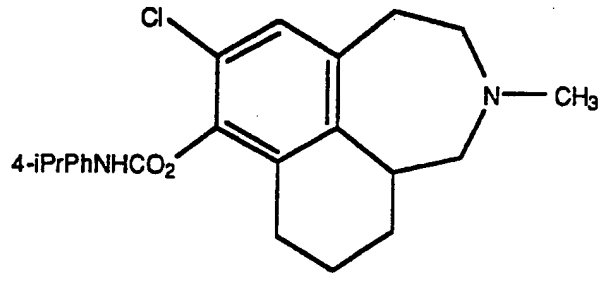




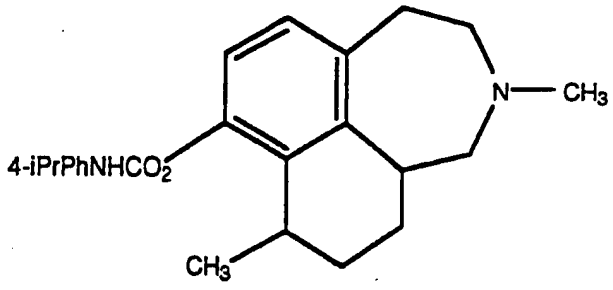

Cl
N
CH3
HO
CH3

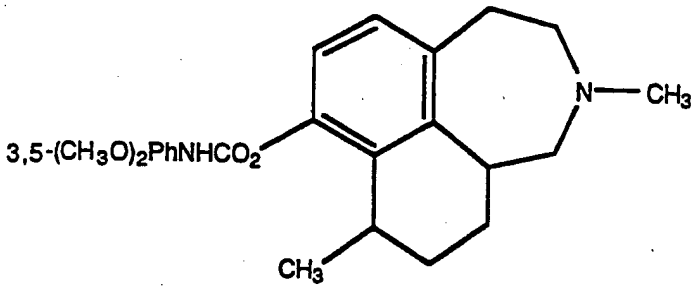

Cl
N
CH3
HO
CH3
H

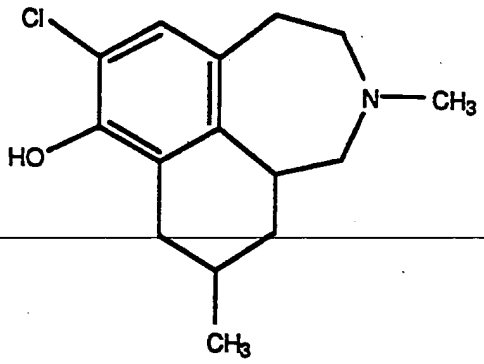

Cl
N
CH3
HO
H
CH3


Cl
N
CH3
4-iPrPhNHCO2

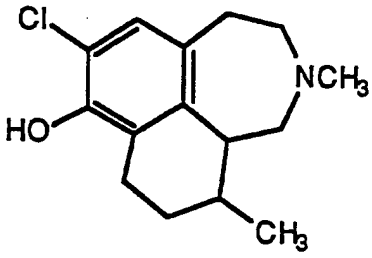
5

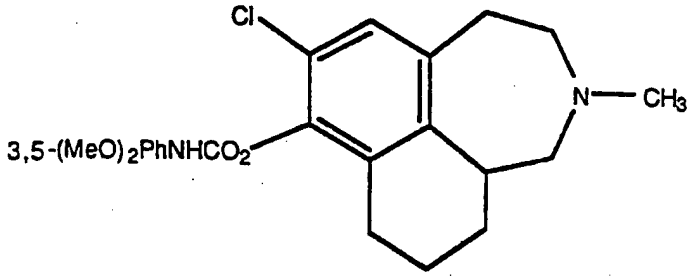

N
CH3
4-iPrPhNHCO2
CH3


3,5-(CH3O)2PhNHCO2
N
CH3
CH3

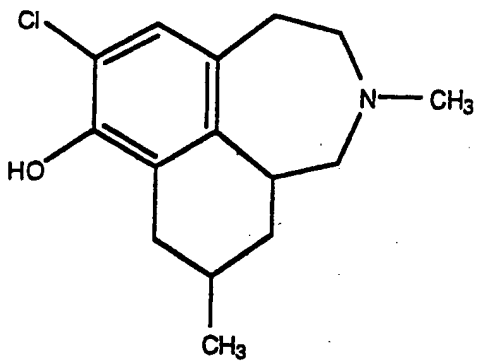

Cl
HO
N
CH3
CH3

5


Cl
HO
NCH3
CH3

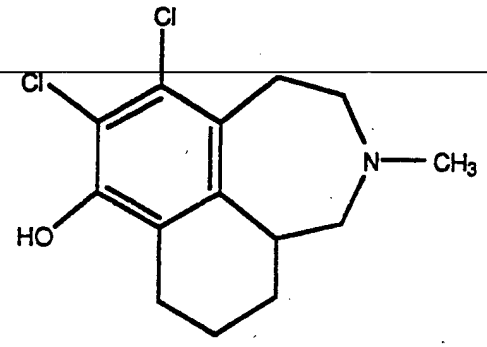

Cl
3,5-(MeO)2PhNHCO2
N
CH3

and



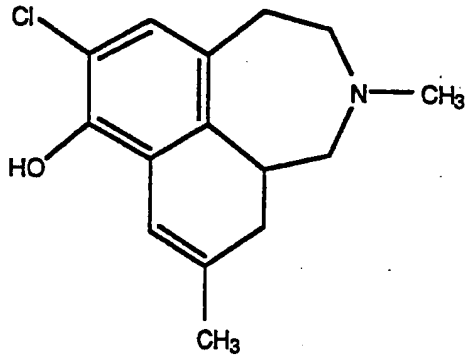
or a pharmaceutically acceptable salt of such a compound.

4. A compound according to claim 1 having the structural formula



or a pharmaceutically acceptable salt thereof.

5. A compound having the structural formula

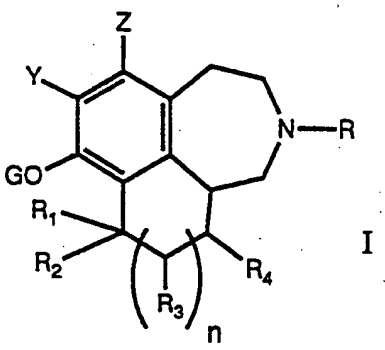


II

or a pharmaceutically acceptable salt thereof.

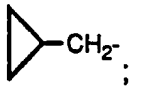
6. A pharmaceutical composition comprising as an active ingredient a compound of formula I or formula II in association with a suitable pharmaceutical carrier.

7. The use of a compound of formula



I

or a pharmaceutically acceptable salt thereof, wherein

R represents H, alkyl, allyl or  ;

n represents 0 or 1;

R_1 and R_2 may be the same or different and each independently represents H, OH, C_1-C_4 alkyl or Ar, with the proviso that

R_1 and R_2 may not both be OH, and with the further proviso that when n is 0, R_1 is C_1-C_4 alkyl or Ar, R_2 is CH_3 and R_4 is H;

R_3 and R_4 may be the same or different and each independently represents H or C_1-C_4 alkyl;

G represents H, $(R_5,R_6)NCO$- or ArNHCO-;

R_5 and R_6 may be the same or different and each independently represents H, C_1-C_4 alkyl, or Ar;

Ar represents phenyl or substituted phenyl;

Y and Z may be the same or different and each independently represents H, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, or C_1-C_4 haloalkyl,

or a compound of formula II

for the manufacture of a medicament for treating psychoses.

8. The use of a compound of formula I or formula II for the manufacture of a medicament for treating drug dependence.

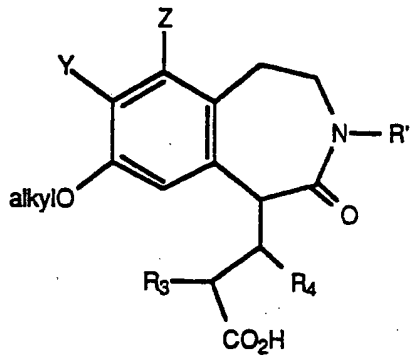
9. The use of a compound of formula I or formula II for the manufacture of a medicament for treating a mammal suffering from a D1 dependent neurological disorder.

10. The use of a compound of formula I or formula II for the manufacture of a medicament for providing analgesia in a mammal.

11. A process for the preparation of a pharmaceutical composition as claimed in claim 1 which comprises admixing a compound as claimed in claim 1 with a pharmaceutically acceptable carrier.

12. A process for the preparation of a compound of formula I set forth in claim 1, which process comprises a process selected from the following processes i, ii, iii, iv, and v:

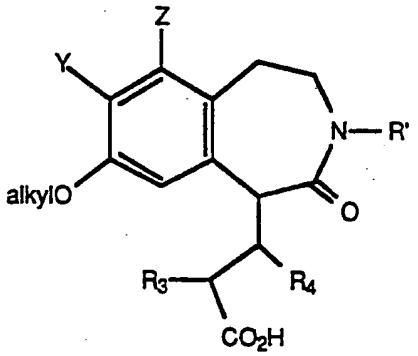
i) cyclizing a compound of formula



B'

wherein Y, Z, R_3 and R_4 are as defined in claim 1, and alkyl is a straight or branched, saturated hydrocarbon chain having from 1 to 8, preferably from 1 to 6, carbon atoms;

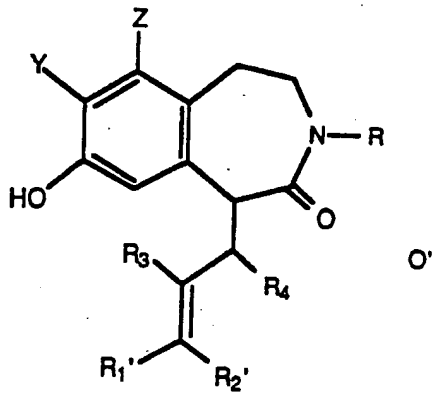
in the presence of a cyclizing agent at a temperature up to the reflux temperature of the reaction mixture and reducing the resulting compound of formula



B'

in the presence of a reducing agent and a solvent at temperatures up to the reflux temperature of the reaction mixture, and

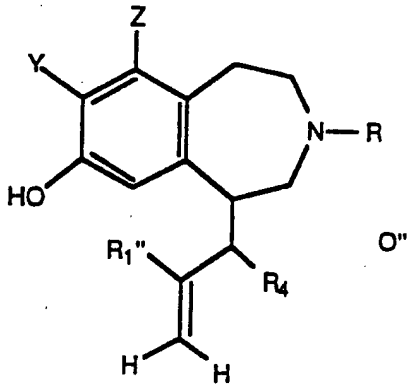
ii) cyclizing a compound of formula



wherein R_1, R_3, R_4, Y, Z are as defined in claim 1, and R_1' and R_2' are are the same as R_1 and R_2 respectively as previously defined, but with the proviso that R_1' and R_2' cannot both be H

in the presence of a cyclizing agent, and

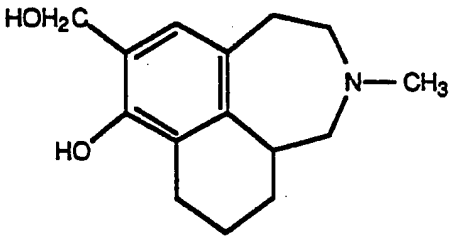
iii) cyclizing a compound of formula



wherein R, Y, and Z are as defined in claim 1, and R_1" is C_1-C_4 alkyl or Ar

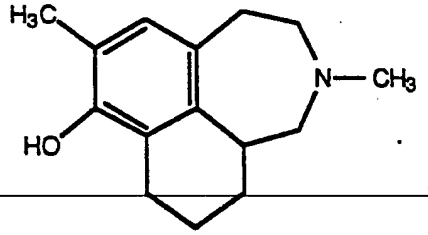
in the presence of a cyclizing agent, and

iv) hydrogenating the compound of formula



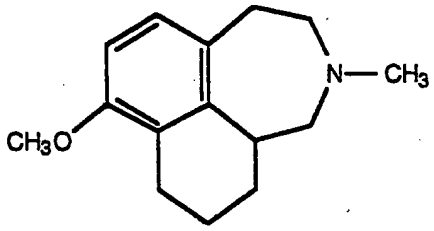
K

in the presence of a hydrogenation agent and a solvent, to obtain the compound of formula



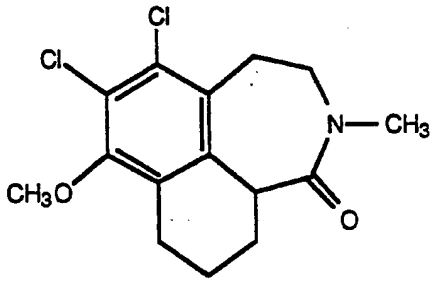
L, and

v) chlorinating the compound of formula



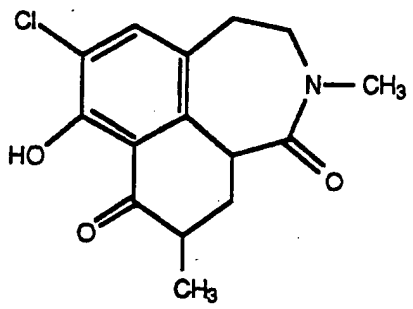
F

in the presence of a chlorinating agent and a solvent, to obtain a compound of formula



G

13. A process for the preparation of the compound of formula II set forth in claim 5, by reducing the compound of formula



in the presence of a reducing agent and a solvent, and chromatographically separating the compound of formula II.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/06705

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D223/14; C07D223/32; A61K31/55

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
Y	US,A,4 957 914 (R.D. CLARK ET AL.) 18 September 1990 see the whole document	1-13
Y	EP,A,0 285 919 (SCHERING CORPORATION) 12 October 1988 cited in the application see the whole document	1-13

[10] Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16 DECEMBER 1991	[illegible]
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	ALLARD M.S.

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9106705 SA 51534

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 16/12/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-4957914	18-09-90	None		
EP-A-0285919	12-10-88	AU-A-	1596488	02-11-88
		EP-A-	0357641	14-03-90
		JP-T-	2502723	30-08-90
		WO-A-	8807526	06-10-88
		US-A-	5015639	14-05-91